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Approximately, 12 million Americans struggle with the bothersome effects of tinnitus to a degree that interferes with their daily activities and quality of their lives. Lacking a clear definition of the origin and mechanism of tinnitus hinders the process of finding validated cure for this debilitating condition. Up until now the role of the central auditory system in tinnitus generation is not completely understood. Perception of tinnitus in normal hearing subjects and persistence of tinnitus after complete ablation of the auditory nerve triggered the current shift in the cause of tinnitus generation from the peripheral source to the central auditory processing source. Multitudinous pathologies are associated with tinnitus perception. Tinnitus perception has also been reported in normal hearing subjects after a brief period of silence. However, there is informational gap regarding the possible changes in the central auditory nervous system associated with tinnitus perception in normal hearing subjects after a brief period of silence.

Therefore, the purpose of this study was to examine the effect of silence and tinnitus perception on the central auditory system using auditory evoked potentials (AEPs). Another purpose was to examine the prevalence of tinnitus perception as a result of silence exposure in the study sample while controlling for directed auditory attention.

Sixty female subjects with normal hearing between ages of 18 to 40 years old participated in the study. Behavioral audiometric measures were administered to confirm eligibility for participation. AEPs were measured before and after 10 minutes of silence exposure. Repeated measures ANOVA were used to examine any group difference as a result of tinnitus perception as well as the effect of silence on the auditory system.

The results showed that 55% of the subjects perceived tinnitus like sounds during silence exposure. Subjects in the tinnitus group did have statistically significant larger AMLR Na/Pa amplitude in both pre-silence and post-silence recordings. There was no statistically significant difference in ABR wave V latency or amplitude as a result of tinnitus perception. The results revealed statistically significant increase of contralateral wave V latency and approached significant levels on the ipsilateral recordings as a result of silence exposure.

These findings support the notions of the previous research that normal auditory systems are producing low-level tinnitus-like sounds, which can be perceived by individuals in a sufficiently quiet environment. The results indicate the presence of increased neural activities at the level of AMLR Na/Pa generators in subjects who perceived tinnitus compared with subjects who did not perceive tinnitus. Therefore, the results of the study support the notion that tinnitus is a central auditory processing phenomenon.

EFFECTS OF SILENCE ON THE PERCEPTION OF TINNITUS AND
AUDITORY EVOKED RESPONSES

by

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APPROVAL PAGE

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TABLE OF CONTENTS

	Page
LIST OF TABLES	vi
LIST OF FIGURES	vii
CHAPTER	
I. INTRODUCTION	1
Statement of the Problem	1
Purpose of the Current Study	6
II. REVIEW OF THE LITREATURE	8
Tinnitus Definition and Prevalence	9
Causes of Tinnitus	10
Theories of Tinnitus Generation	10
Tinnitus and Auditory Deprivation	15
Tinnitus Perception and Subject Factors	20
Auditory Evoked Potentials (AEPs)	24
Auditory Brainstem Response	25
Auditory Middle Latency Response	26
Neurogenerators of AEPs	27
Subject Factors for ABR Waveform	29
Subject Factors for AMLR Waveform	31
AEPs and Tinnitus	33
Purpose of the Current Research	37
Research Hypotheses	38
Research Questions	39
III. METHODS	40
Participants	40
Materials	42
Instrumentation and Equipment	42
Procedures	44
Statistical Designs and Analysis	49

IV. RESULTS	53
General Descriptive and Behavioral Data	53
Physiological Data Analysis	60
ABR Wave V Analysis.....	61
Effect of Silence on ABR Wave V	63
Effect of Tinnitus Perception on ABR Wave V	65
AMLR Analysis.....	70
Effect of Silence on AMLR Measurements	74
Effect of Tinnitus Perception on AMLR Measures	76
V. DISCUSSION	85
Effect of Silence on The Emergence of Tinnitus Perception	86
Effect of Silence on the Neural Pattern of the CANS	88
The Emergence of Tinnitus Perception and AEPs.....	92
Conclusions.....	96
Limitation and Future Direction	96
REFERENCES.....	98
APPENDIX A. GENERAL HEALTH QUESTIONNAIRE.....	110
APPENDIX B. SILENCE QUESTIONNAIRE.....	114

LIST OF TABLES

	Page
Table 1. General Demographics	54
Table 2. Frequency of Auditory Sounds Perceptions	58
Table 3. Tinnitus Onset and Location.....	59
Table 4. Types of Tinnitus Sounds Heard by Subjects During Silence	60
Table 5. Ipsilateral Mean ABR Wave V Latency and Amplitude	62
Table 6. Contralateral Mean ABR Wave V Latency and Amplitude	63
Table 7. Within Subjects Effect of Silence for Ipsilateral ABR Measures	64
Table 8. Within Subjects Effect of Silence for Contralateral ABR Measures.....	65
Table 9. Between Subjects Effect of Tinnitus Perception on Ipsilateral ABR Measures	66
Table 10. Between Subjects Effect of Tinnitus on Contralateral ABR Measures	66
Table 11. Ipsilateral AMLR Results for Tinnitus and Non-Tinnitus Groups for Pre-Silence and Post-Silence Conditions	72
Table 12. Contralateral AMLR Results for Tinnitus and Non-Tinnitus Groups for Pre-Silence and Post-Silence Conditions	74
Table 13. Within Subjects Effect of Silence for Ipsilateral AMLR Measures	75
Table 14. Within Subjects Effect of Silence for Contralateral AMLR Measures	76
Table 15. Between Subjects Effect of Tinnitus Perception on Ipsilateral AMLR Measures	77
Table 16. Between Subjects Effect of Tinnitus Perception on Contralateral AMLR Measures	78

LIST OF FIGURES

	Page
Figure 1. Auditory Evoked Potentials Waveforms	25
Figure 2. Neuroanatomical Correlates of AEPs	28
Figure 3. Electrode Montage used for AEPs Measurements	46
Figure 4. Illustration of the Study Procedures	48
Figure 5. Illustration of the AMLR Na/Pa Latency and Amplitude Measurements	50
Figure 6. Right Ear Mean Thresholds for Tinnitus and Non-Tinnitus Groups	56
Figure 7. Left Ear Mean Thresholds for Tinnitus and Non-Tinnitus Groups	57
Figure 8. Estimated Marginal Means of Ipsilateral ABR Wave V Latency	67
Figure 9. Estimated Marginal Means of Ipsilateral ABR Wave V Amplitude	68
Figure 10. Estimated Marginal Means of Contralateral ABR Wave V Latency	69
Figure 11. Estimated Marginal Means of Contralateral ABR Wave V Amplitude	70
Figure 12. Estimated Marginal Means of Ipsilateral Na Latency	79
Figure 13. Estimated Marginal Means of Ipsilateral Pa Latency	80
Figure 14. Estimated Marginal Means of Ipsilateral Na/Pa Amplitude	81
Figure 15. Estimated Marginal Means of Contralateral Na Latency	82
Figure 16. Estimated Marginal Means of Contralateral Pa Latency	83
Figure 17. Estimated Marginal Means of Contralateral Na/Pa Amplitude	84

CHAPTER I

INTRODUCTION

Statement of the Problem

Tinnitus is a phantom sensation of hearing a sound in the absence of an actual external physical auditory stimulus (Møller, 2016). Tinnitus is considered one of the most common and debilitating otologic problems, as it causes various somatic and psychological disorders that interfere with an individual's quality of life (Han, Lee, Kim, Lim, & Shin, 2009). Tinnitus affects approximately 50 million adults in the US. Of those affected, around 12 million seek medical care, as their tinnitus is distressing enough to interfere with their everyday activities (Newman, Sandridge, & Jacobson, 2014). Among those individuals experiencing tinnitus, around 2-3 million report severely debilitating symptoms that include depression, anxiety, and insomnia (Atik, 2014; Shargorodsky, Curhan, & Farwell, 2010).

Tinnitus is not a disease in itself but it is a symptom of a variety of underlying disorders (Han et al., 2009; Jastreboff, 1990). Currently, the exact mechanism of tinnitus is not fully understood. However, knowledge regarding its etiology suggests that tinnitus might result from a variety of causes including

otologic disorders, neurologic causes, and certain medications (Han et al., 2009; Zenner et al., 2017).

Otologic causes of tinnitus include presbycusis, otosclerosis, otitis media, impacted cerumen, sudden deafness, Meniere's disease, and noise-induced hearing loss, with noise exposure believed to be the most common cause for tinnitus (Han et al., 2009). Neurologic causes of tinnitus include multiple sclerosis, vestibular schwannoma, and other cerebellopontine-angle tumors (Han et al., 2009). Tinnitus can also result as a side effect of some oral medications such as salicylates, non steroidal anti-inflammatory drugs, aminoglycoside antibiotics, loop diuretics, and chemotherapy agents (Zenner et al., 2017).

Understanding the pathophysiology of chronic tinnitus is essential for developing effective treatment of this disorder, yet this is still challenging due to the subjective nature of tinnitus and the multitudinous nature of the underlying disorders comprising tinnitus (Wu, Stefanescu, Martel, & Shore, 2016). Given the heterogeneity observed in the tinnitus population, it may be considered that no single theory, model or hypothesis will explain the presence of tinnitus in all affected individuals (Baguley, 2002).

Originally, cochlear abnormalities were thought to be the initial source of tinnitus generation as a result of the common association between tinnitus and peripheral hearing loss such as noise exposure, ototoxic drug intake, and age related hearing impairment (Jastreboff, 1990; Tonndorf, 1981, 1987). Currently,

more evidence of the involvement of the neuroplastic changes in the central auditory nervous system (CANS) in tinnitus generation has been identified. The evidence of central involvement in chronic tinnitus include the perception of tinnitus in normal hearing subjects without cochlear damage and the persistence of tinnitus after ablation of the cochlear nerve (Atik, 2014; McFerran & Phillips, 2007; Wu et al., 2016).

Silence-induced tinnitus is one of the theories of tinnitus generation. Several studies examined the prevalence of tinnitus-like activity in apparently normal hearing subjects after exposure to a period of silence in a sound treated room (Del Bo et al., 2008; Heller & Bergman, 1953; Knobel & Sanchez, 2008; Tucker et al., 2005). The results of these studies revealed a high prevalence of tinnitus-like perception in such conditions. These findings indicate that tinnitus is a physiological phenomenon in the human auditory system that is usually masked by the ambient noise in the surrounding environment (Heller & Bergman, 1953). Hence, in these cases, tinnitus might emerge as a result of two mechanisms. The first mechanism is the increase in the gain within the auditory pathways resulting from low-level signals reaching the ear, which in turn leads to an increase in the sensitivity of the neurons of the auditory pathway, and can activate neural plasticity (Møller, 2011). The second mechanism is that the strength of any signal within the nervous system is related to its contrast with background neural activity; hence, lack of environmental masking sounds can result in tinnitus perception (Tucker et al., 2005).

Tinnitus perception in normally hearing individuals emphasizes the role of the central auditory nervous system in tinnitus generation and perception. Auditory evoked potentials (AEPs) are usually used to measure the brain's responses to auditory stimuli (Hall, 2007). Thus, AEPs can be used to investigate any possible changes in the central pathways associated with tinnitus perception. AEPs are divided into early, middle, and late potentials in terms of the time epochs in which they occur relative to the onset of the stimulus. Several studies examined the changes in the central auditory pathway in normal hearing subjects with and without tinnitus (Gu, Herrmann, Levine, & Melcher, 2012; Kehrle et al., 2008; Nemati, Faghih Habibi, Panahi, & Pastadast, 2014). Results from these studies demonstrated enhancement in the amplitude of the auditory brainstem responses (ABR) waves III and V, which indicate involvement of the central auditory system up to the level of the brainstem in tinnitus generation.

The auditory middle latency response (AMLR) represents a complex generating system that involves centers in the auditory pathway from the midbrain to the cortex as well as regions that process multimodal stimuli such as the reticular formation. Emerging evidence reveals that excitatory-inhibitory imbalance and changes in neuronal activity in different parts of the auditory pathway, including the dorsal cochlear nucleus, inferior colliculus, thalamus and/or auditory cortex underlie tinnitus pathology (Møller, 2011). Since these areas mostly contribute to the generation of AMLR waveform, AMLR can be a

promising tool for detection of any possible changes in these areas associated with tinnitus perception.

Both human and animal research studies indicate the contribution of multiple brain areas to AMLR generation. The most likely contributors to AMLR waveform generations include auditory cortex, medial geniculate body, mesencephalic reticular formation and the inferior colliculus (McGee, Kraus, Comperatore, & Nicol, 1991).

Given the evidence that supports the central origin for tinnitus generation and the suggested related anatomical origin of AEPs, AEPs can be an optimal electrophysiological test that can detect changes in the central auditory system as a result of tinnitus.

Several factors can affect AMLR measurement such as age, gender, and race. Thus, it is important to control for such factors. Advanced age related changes on AMLR measures include poor waveform morphology and increased Pa amplitude and latency (Burkard, Eggermont, & Don, 2007; Hall, 2007). This unexpected increase in AMLR wave amplitude while other brain functions decline with advanced age can be explained by the decrease in the inhibitory connections mediated by gamma-amino butyric acid within the auditory system with age (Picton, 2011).

The effect of gender on AMLR measures is posited to interact with the effects of aging on the auditory system (Hall, 2007). However, the effect of

gender on the AMLR measures is unclear with reported smaller amplitude and longer latencies in males versus females (Hall, 2007).

Similarly, a variety of factors can affect tinnitus perception such as gender, age, hearing loss, physiological condition, and race. The literature on the effect of gender and age on the perception and reaction to tinnitus is controversial. Some studies revealed gender differences with more perception and reaction to tinnitus reported for females (Stouffer & Tyler, 1990; Welch & Dawes, 2008). The effects of age on tinnitus perception and annoyance have been reported to be more pronounced in older populations (Hiller & Goebel, 2006). However, Pinto, Sanchez, and Tomita (2010) demonstrated no influence of age or gender on tinnitus perception in their sample. Tucker and colleagues (2005) reported a statistically significant difference between African Americans and Caucasians in tinnitus perception following exposure to a silence period, with Caucasians more prone to tinnitus than African Americans. The authors also reported no influence of gender on tinnitus perception after silence exposure in their studied sample.

Purpose of the Current Study

None of the previous studies on silence-induced tinnitus examined the central auditory processing changes resulting from auditory deprivation due to silence exposure objectively, using AEPs (e.g. ABR and AMLR). The current study hypothesized that auditory deprivation due to silence exposure will induce increased activities within the central auditory system that can be measured using AEPs (ABR and AMLR). Thus, the current study was designed to examine

the impact of silence-induced tinnitus-like perception on the AMLR waves Na-Pa and ABR wave V amplitude and latency, while controlling for the effects of age, gender, and normal hearing threshold.

CHAPTER II

REVIEW OF THE LITERATURE

Auditory phantom perception of a sound in the absence of an actual external acoustic stimulus is known as tinnitus (Eggermont & Roberts, 2004). Tinnitus is a challenging otologic problem that can have a huge impact on the quality of life of its sufferers. In most cases, this phantom perception is associated with hearing loss that is either induced by aging or noise exposure. Nevertheless, tinnitus perception has been reported in subjects with normal hearing, which represents a challenge to the current theories for tinnitus generation. Despite the presence of a variety of procedures that enable tinnitus sufferers to adapt and modulate their tinnitus perceptions, to date there is no treatment that can cure or eliminate the tinnitus itself. Understanding the pathophysiology of tinnitus is essential for developing such treatments. Thus, the aim of this literature review is to elucidate this complex phenomenon of tinnitus, paying special attention to the identification of systems and networks underlying tinnitus generation. Accordingly, the following literature review encompasses four main topics: 1) tinnitus, 2) tinnitus and auditory deprivation, 3) auditory evoked potentials including (auditory middle latency and auditory brainstem responses), and 4) auditory evoked potentials as an objective measure for tinnitus

Tinnitus Definition and Prevalence

Tinnitus, derived from the Latin word “tinnire” which means, “to ring”, is the perception of noise in the absence of an acoustic stimulus (Swain, Nayak, Ravan, & Sahu, 2016). Tinnitus is considered one of the most common and distressing otologic problems that can cause various somatic and psychological disorders that interfere with an individual’s quality of life. In the majority of cases, tinnitus is subjective, perceived only by the patient. Thus, diagnosis and monitoring of tinnitus rely primarily on self-report (Shargorodsky et al., 2010).

According to the World Health Organization (WHO), approximately 15% of the world population experiences tinnitus. This prevalence increases to 33% among individuals over 60 years of age (Geocze, Mucci, Abranches, Marco, & Penido, 2013). Reaction to tinnitus varies among those who experience this phantom perception, with the majority of tinnitus subjects able to habituate to the tinnitus perception. In about 25% of subjects with tinnitus, the condition is annoying and interferes with daily activity (Atik, 2014). The lack of habituation to the tinnitus perception is associated with personality traits or symptoms of depression. Subjects with tinnitus report a variety of additional symptoms including anxiety, irritability, agitation, stress, depression and/or insomnia (Geocze et al., 2013; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011).

Causes of Tinnitus

Understanding the pathophysiology of tinnitus is essential for developing effective treatment; however, this is hindered by the subjective nature of the auditory perception of tinnitus (Wu et al., 2016). Tinnitus does not represent a disease itself, but instead is a symptom of a variety of complex underlying diseases. Han and collauges (2009) summarized a variety of underlying diseases that are associated with tinnitus, which include:

1. Otologic disorders such as noise-induced hearing loss, presbycusis, otosclerosis, Meniere's disease, and other causes of hearing loss.
2. Neurologic disorders such as head injury, multiple sclerosis, vestibular schwannoma and other cerebellopontine-angle tumors.
3. Infectious diseases such as otitis media, meningitis, and other infectious or inflammatory, processes that affect hearing.
4. Oral medications, such as salicylates, non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics, loop diuretics, and chemotherapy agents.

Theories of Tinnitus Generation

Hypotheses regarding mechanisms of tinnitus generation abound. Given the heterogeneity observed in the tinnitus population, no single theory, model or hypothesis can fully explain the presence of tinnitus in all those who are affected (Baguley, 2002). Baguley (2002) also noted that the mechanisms for tinnitus are not mutually exclusive, thus multiple mechanisms may be present in an individual

with tinnitus. Bauer (2004) categorized theories of tinnitus pathophysiology into three main categories:

- 1) Theories that emphasize aberrant peripheral neural activity,
- 2) Theories that focus on central neural sources, and
- 3) Theories that view central dysfunction as interacting with, and amplifying, a peripheral source of abnormal input.

Peripheral theories of tinnitus generation. The association between tinnitus and hearing loss comprised early tinnitus theories to emphasize the role of the peripheral auditory system in tinnitus generation. The possible peripheral generators of tinnitus include:

- 1) Spontaneous Otoacoustic Emissions (SOAEs): Kemp in 1978 first discovered these small acoustic signals that presumed to be generated by the electro-motile activity of the OHCs of the cochlea. These activities are usually inaudible, but they can become audible and perceived as tinnitus (Kemp, 1978). However, several pieces of evidence oppose SOAEs as a source of tinnitus (Baguley, 2002). First, despite that 38–60% of normal-hearing adults have measurable SOAEs; the majority of those individuals are not aware of the presence of these OHCs activities. Secondly, even when SOAEs do occur in the ear of a tinnitus patient, they rarely correspond to the judged frequency of the tinnitus. Lastly, aspirin (salicylate) largely abolish SOAEs, but tinnitus perception is not generally improved by salicylate. Conversely, aspirin might worsen tinnitus

perception with increased risk of ototoxic hearing loss and the possible generation of new tinnitus perceptions.

- 2) Hair cell damage: Cochlear hair cell damage results in decoupling of the stereocilia from the tectorial membrane with subsequent development of increased noise from molecular motion within the hair cells that can be perceived as tinnitus (Tonndorf, 1981).
- 3) Discordant damage of IHC and OHC: This theory proposes that tinnitus is induced by the discordant dysfunction of damaged OHCs and intact inner hair cells (IHCs) of the organ of Corti (Jastreboff, 1990). Usually OHCs are more liable to damage than IHCs, which results in the dis-inhibition of neurons in the dorsal cochlear nuclei (DCNs). Subsequently, spontaneous activity will increase when neurons in the DCN receive excitation from IHCs, but not from the damaged OHCs, which is then perceived as tinnitus. Discordant theory explains perception of tinnitus in normal hearing individuals because usually damage to 30% of the outer hair cells is required before it induces apparent hearing loss on the audiogram (Han et al., 2009).
- 4) Biochemical model of peripheral tinnitus: This model is based partly on the clinical observation that adult humans with distressing tinnitus have experiences of agitation, stress, and anxiety; and partly on cochlear neurochemistry. Sahley & Nodar (2001) postulated that endogenous dynorphins potentiate the excitatory properties of glutamate at NMDA

receptor. This in turn leads to the production of synchronous auditory neural discharge in quiet that is perceived as real sound.

- 5) Cross-talk between hair cells or VIII nerve fibers: This theory posits that tinnitus perception is based on the occurrence of 'cross-talk' between demyelinated auditory nerve fibers or hair cells where there was breakdown of electrical insulation between them. This loss of insulation could occur after acoustic neuroma and other retro-cochlear pathologies and result in increased phase correlation of the spontaneous activity of different fibers. These activities ultimately become phase-locked with each other, leading to abnormal pulse generation (Jastreboff, 1990).

Central theories of tinnitus generation. Recently, theories of tinnitus generation have shifted toward central mechanisms, as several clinical observations suggested that tinnitus might result from aberrant central neural activity alone (Bauer, 2004). These observations include persistent tinnitus perception after complete eighth nerve section and the perception of tinnitus in subjects with normal hearing thresholds. The central mechanisms proposed to account for the generation of tinnitus-related activity is thought to be triggered by a reduction in cochlear activity, not necessarily cochlear damage (Bauer, 2004). For example, conductive hearing loss, which preserves hair cells and cochlear fibers, has been reported to induce tinnitus (Noreña, 2015; Noreña & Farley, 2013).

Brainstem plasticity and tinnitus generation. It is widely accepted that all levels of the nervous system are to varying degrees, involved in tinnitus manifestation (Eggermont & Roberts, 2004; Gu et al., 2012; Kaltenbach, 2000; Saunders, 2007; Schaette & McAlpine, 2011; Wu et al., 2016). In many cases, the proposed central models and hypotheses do not preclude a role for the cochlea, but have the central changes in the auditory pathway as their primary concern for neural mechanisms of tinnitus generation and persistence (Møller, 2007).

Auditory Neuroplasticity is the capacity of the brain to reorganize its neural networks on the basis of new experience. These neuroplastic changes may be positive and adaptive as with learning or memory or in the compensation after brain injury, which results in new neuronal networks that restore normal function. Alternatively, neuroplastic changes might be maladaptive leading perhaps to an imbalance in excitatory and inhibitory events in the brain. Consequently, tinnitus might be a consequence of such maladaptive neuroplastic brain alterations (Saunders, 2007).

According to the auditory neuroplasticity theory, reduced input to the auditory nerve either through reduced spontaneous firing rate (SFR) or deafferentation of auditory nerve fibers (AN) fibers are essential to trigger changes at various levels of the central auditory pathway (Eggermont & Roberts, 2004; Schaette & McAlpine, 2011). The target sites for these changes include mainly the dorsal cochlear nucleus, where diminished auditory nerve input

initiates hyperactivity of DCN neurons, which then spreads to higher areas (Gu et al., 2012; Wu et al., 2016). Other possible sites include the inferior colliculus, the primary auditory cortex in the temporal lobe, and the auditory association cortex (Kaltenbach, 2000; Saunders, 2007). The imbalance between excitation and inhibition can also lead to an increase in the neural synchrony and reorganization of the cortical tonotopic map (Eggermont, 2006).

Tinnitus and Auditory Deprivation

Clinically, many patients report experiencing tinnitus in the absence of perceived hearing loss and a normal audiogram (Schaette & McAlpine, 2011). Tinnitus with normal hearing presents a challenge to the model of tinnitus generation that emphasizes the role of cochlear damage in tinnitus generation. The perception of tinnitus in normal hearing subjects indicates that the source of tinnitus generation is not limited to the peripheral auditory system and provides evidence for the role of the central auditory system in tinnitus generation. Thus, central auditory changes might be a consequence of different forms of auditory deprivation that can result not only from pathologies of the ear such as otitis media, but also from lack of environmental sounds. Subsequently, auditory deprivation can cause interruption of the input from the ear to the central auditory system and hence induce neural plasticity. The subsequent changes in the function of the central nervous system can cause some forms of tinnitus-like perception (Møller, Langguth, DeRidder, & Kleinjung, 2010).

The surrounding acoustical environment has been indicated to have a significant impact on tinnitus perception, which further emphasize the role of the central auditory system in tinnitus generation. Animal studies have revealed that reorganization of tonotopic map of the auditory cortex, as well as increased spontaneous firing rate and neural synchrony, are more pronounced in quiet environments compared with sound-enriched environments (Noreña & Eggermont, 2006). Clinically, many subjects with tinnitus report that their tinnitus perception is more prominent in quiet settings and less perceived in sound-enriched environments. This denotes that tinnitus may represent ongoing activities within the auditory system, and that surrounding environmental sounds play an important role in mitigating the perception of these activities. Thus, tinnitus signals could exist in each individual network at a very low strength that can only be perceived when the surrounding background sounds are low (Jastreboff, 2007).

Temporary tinnitus perception as a result of silence exposure has been demonstrated in healthy persons with normal hearing when the ambient noise level is low. Heller and Bergman (1953) employed a group of self-reported normal hearing subjects (based only on their history of absence of hearing loss); and a control group of hard of hearing subjects (based on their hearing history and audiologic evaluations). Subjects in both groups were exposed to five minutes of silence in a soundproof room and were instructed to make notes of any sounds detected during this period. There was no suggestion given about

the source of sound. Heller and Bergman found that approximately 94% of the apparently normal hearing healthy adults who participated in the study experienced tinnitus. The authors noted that perception of tinnitus-like sounds in apparently normal hearing subjects when placed in a sound-proof room were similar to the perception of tinnitus-like sounds experienced by the subjects with diagnosed hearing loss. As a result of these findings, Heller and Bergman concluded that tinnitus is a physiological phenomenon in an intact auditory apparatus that is usually masked by the ambient noise in the surrounding environment.

Based on Heller and Bergman's theory that tinnitus is a physiological phenomenon that can result from the lack of environmental masking sounds, Tucker and colleagues (2005) investigated the impact of race and gender on the emergence of tinnitus in normal hearing young adults when they were exposed to a period of silence. In this study, 120 normal hearing young adults with an age range of 18 - 30 years were studied. Tucker and colleagues examined 60 males and 60 females within both gender groups; 40 participants were Caucasian and 20 participants were African American. All subjects had normal peripheral hearing. Subjects were placed in a sound booth for 20 minutes of silence exposure and then were asked to report any perceived sounds. Results of the study showed that there was no significant difference in tinnitus perception due to gender, but there was a significant difference as a result of race. Tinnitus was perceived more commonly among Caucasian listeners than African American

listeners, with all listeners reporting perceiving tinnitus very early (within four minutes) of the 20-minute silence exposure. The overall tinnitus perception in this study was 64% of all listeners, which is lower than that reported by Heller and Bergman. This difference might result from the different age group in both studies and the possibility of the presence of hearing loss in the Heller and Bergman study, as they did not measure hearing thresholds in the normal subject group.

Del Bo and colleagues (2008) also investigated tinnitus as a common subclinical condition of the general population when confined in a very silent environment as well as the effect of auditory suggestion on such perceptions. In this study, Del Bo and colleagues utilized distortion product otoacoustic emissions (DPOAEs) as a measure of activity of the outer hair cells within the cochlea to document normal peripheral auditory system functioning and absence of minimal hearing loss in all participants. Fifty-three young healthy volunteers with normal hearing between the ages of 19 and 29 years participated in this study. All participants had a complete audiologic evaluation that included pure tone audiometry in the frequency range 250-16,000 Hz, impedancemetry, and distortion product otoacoustic emissions (DPOAEs) to confirm their normal hearing. In addition, evaluation of the subjects' high frequency hearing up to 16 kHz was performed to detect any subtle hearing loss that might be a factor in tinnitus perception. All participants in this study were exposed to two sessions of 4 minutes of silence in an anechoic sound chamber. In both sessions the participants were instructed to listen for potential sounds and received a list of

possible sounds that they might experience in the sound chamber. These instructions likely increased their auditory attention to sounds. In the second session a loudspeaker was placed in the sound chamber to increase the suggestion of the presence of sounds. The results of this study reported that 83% of the participants experienced at least one sound when the loudspeaker was not present. This percentage increased to 92% when the loudspeaker was present, which indicate that suggestive mechanisms played only a minor role in perception of tinnitus-like sounds in silence.

This study confirmed the results of the classic experiment of Heller and Bergman (1953) demonstrating that tinnitus-like perception under acoustic deprivation occurs in a thoroughly audiologically tested sample of normally hearing individuals. Thus, silence-induced tinnitus is a stable phenomenon in which the auditory system is continuously generating low intensity sounds, which typically is masked by the environmental noises.

Knobel & Sanchez (2008) also investigated the effect of sustained silence on the emergence of tinnitus in normal hearing subjects with and without selective auditory attention. These authors investigated the role of auditory attention and expectation on tinnitus perception. They theorized that directed auditory attention in silence activates top-down modulation of neural mechanisms lead to increased magnitude and speed of neural activity as a response to directed attention as opposed to suppression of neural activity related to the processing of unwanted information (Knobel & Sanchez, 2008). Sixty-six subjects

with ages ranging from 18 to 65 years participated in this study. All subjects had normal hearing thresholds, normal middle ear functions and normal transient Evoked otoacoustic emissions (TEOAEs). Subjects were seated in a soundproof booth and were asked to perform three consecutive tasks in which the order of presentation was randomly varied across participants. Two of the tasks directed the attention away from the auditory system and one task activated auditory attention. In auditory attention, half of the participants were asked to give oral responses and the other half gave written responses. The results of this study revealed that tinnitus perception in normal adults varied according to different attention conditions with the auditory attention condition producing the highest rate of tinnitus perception at 68.2% of all listeners, which is slightly higher than the 64 % reported by Tucker et al, (2005). Therefore, the findings in Knobel & Sanchez (2008) supported the idea that auditory attention plays an important role for the perception of tinnitus and their results agree with the findings of Heller & Bergman (1953), Tucker et al. (2005), and Del Bo et al. (2008) that normal-functioning auditory systems are constantly producing a low-level tinnitus that is audible only when listeners are in a sufficiently quiet environment. However, none of these studies investigated the potential changes in the central auditory system following auditory deprivation as a result of silence experience.

Tinnitus Perception and Subject Factors

The relations between tinnitus and subject demographic health factors such as age, gender, the presence of hearing loss, and the presence of

psychological comorbidity have been addressed in different studies. These factors play an important role in tinnitus perception and annoyance.

Effect of gender. A number of studies have examined the effect of gender on the prevalence of tinnitus; however, the results of these investigations are controversial. Although some have described a higher prevalence of tinnitus in males (Heller, 2003; Hiller & Goebel, 2006; Lockwood, Salvi, & Burkard, 2002; Seydel, Haupt, Olze, Szczepek, & Mazurek, 2013; Shargorodsky et al., 2010), others have suggested that the prevalence and the degree of tinnitus annoyance are slightly higher among females (Stouffer & Tyler, 1990; Welch & Dawes, 2008). In contrast, other studies have reported no gender effect on tinnitus prevalence (Durai, O’Keeffe, & Searchfield, 2017; Erlandsson & Holgers, 2001; Pinto et al., 2010) .

Effect of age. Demographic studies of subjects’ perception of tinnitus revealed a greater prevalence of tinnitus in older populations than in younger adults and noted an increased tinnitus prevalence with advanced age as a result of presbycusis or age related hearing loss (Baguley, McFerran, & Hall, 2013; Hiller & Goebel, 2006; Lockwood et al., 2002; Shargorodsky et al., 2010).

Effect of race. Several demographic studies that examined the effect of race (based on the subject’s reporting their self-identified race or ethnicity) on tinnitus prevalence noted higher tinnitus prevalence in Caucasians compared with those of African–American populations (Heller, 2003; Lockwood et al., 2002; Shargorodsky et al., 2010; Tucker, 2005).

Directed auditory attention. Top-down modulations of neural activities are responsible for our abilities to selectively attend to relevant stimuli and ignoring the irrelevant ones (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). These mechanisms are initiated by the subject's intention and influenced by directed attention. Thus, directed attention plays an important role in alteration of cerebral cortical functions (Hopfinger & Maxwell, 2005). Therefore, most tinnitus patients report increased awareness of tinnitus sounds when they direct their attention to the tinnitus.

Noise exposure and hearing loss. Various investigations have demonstrated increased tinnitus prevalence in subjects with hearing loss as a result of loud occupational, leisure-time, and firearm noise exposure (Heller, 2003; Lindgren, Wieslander, Dammström, & Norbäck, 2009; Seydel et al., 2013; Shargorodsky et al., 2010).

Personality traits and psychological disorders. Tinnitus perception depends on the presence of the triggering stimulus to the auditory cortex such as loss of cochlear input (Atik, 2014). However, the degree of tinnitus annoyance, impact of tinnitus on daily life, and the ability to adapt to the tinnitus perception varies greatly among individuals with tinnitus. This variation in tinnitus annoyance and adaption indicates a significant association between personality characteristics and tinnitus perception. Several studies investigated potential predisposing psychosocial and personality factors associated with tinnitus (Durai et al., 2017; Langenbach, Olderog, Michel, Albus, & Köhle, 2005; Langguth et al.,

2007; Mucci, Geocze, Abranches, Antúnez, & Penido, 2014). Ziai, Moshtaghi, Mahboubi, & Djalilian (2017) described a strong association between tinnitus perception and psychiatric diseases including depression, stress and anxiety. However, the exact mechanism through which psychiatric diseases such as depression interacts with tinnitus are not fully understood.

Geocze et al. (2013) described three possible mechanisms of the association between depression and tinnitus: 1) depression as one of the factors that worsens tinnitus, 2) tinnitus as a predisposing factor to depression, and 3) tinnitus occurring as a comorbidity in patients with depression. Hence, severe tinnitus and depression have a bidirectional association. Depression can be a predisposing factor that increases the intensity, the discomfort and the intolerance to tinnitus. Conversely, tinnitus can often exacerbate existing or advance depression and anxiety. Dobie (1997) reported that people who become severely distressed and depressed with tinnitus are the ones who have a predilection, whether genetic or acquired during life, to depressive episodes. Thus, positive counseling on tinnitus patients is an important aspect of tinnitus management.

In summary, tinnitus perception necessitates the presence of a physiological or pathological condition that provides a stimulus to the auditory cortex and personal tendency to report this tinnitus perception. Personality traits can act as potential moderators of tinnitus perception and annoyance. Thus, it is

important to control for such factors when examining the impact of tinnitus on the central auditory system.

Auditory Evoked Potentials (AEPs)

AEPs are non-invasive measurements evoked by sound that evaluate the integrity of the auditory pathways. AEPs are a sequence of 15 waves that begin within a millisecond or two following the stimulus onset and continue for about 500 msec post-stimulus (Kraus, Ozdamar, Hier, & Stein, 1982). AEPs are classified according to their latency into: 1) short latency that occur within 1-10 msec following a stimulus onset; 2) middle latency that occur within 15-70 msec following a stimulus onset; 3) late latency that occur after 75 msec following a stimulus (Picton, 2011). Presumably, these AEPs waveforms reflect neural activity from the auditory periphery to the cortex. Thus, they can be used to detect any central changes associated with tinnitus. Figure 1 represents auditory evoked potentials waveforms peaks related to their latency, adopted from (Picton, 2011).

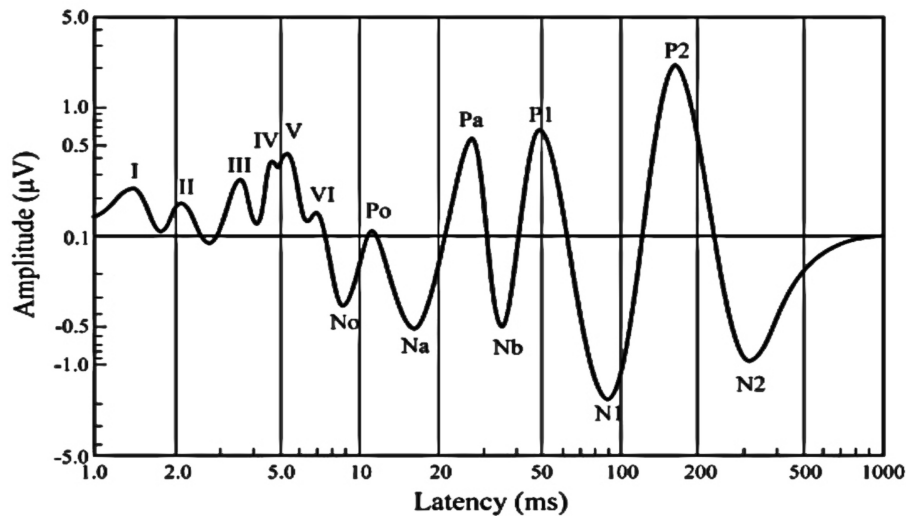


Figure 1. Auditory Evoked Potentials Waveforms.

Auditory Brainstem Response

Auditory Brainstem Response (ABR) is a part of the AEPs that occurs within the first 10 msec following the stimulus onset. Jewett and Williston first described ABR in 1971 as a series of positive waves that are usually numbered with Roman numerals I to VII (Picton, 2011). Hall (2007) summarized the anatomic generators and latencies of the ABR waves:

1. Wave I: Distal portion of the auditory nerve in the cochlea occurring at about 1.69 msec.
2. Wave II: Proximal portion of the auditory nerve as it enters the brain stem occurring at about 2.78 msec.
3. Wave III: Cochlear nucleus occurring at about 3.77 msec.
4. Wave IV: Superior olivary complex occurring at about 4.97 msec.

5. Wave V: Lateral lemniscus as it terminates in the inferior colliculus occurring at about 5.63 msec. Wave V is the largest of the ABR positive waves, has a typical peak-latency of 5.6 msec when evoked by a click at 70 dB nHL (Picton, 2011).

Auditory Middle Latency Response

Auditory middle-latency responses (AMLR) are part of the AEPs that occur after ABR and before ALR between 15-70 msec following a stimulus onset. When AMLR was first described by Geisler in 1958, he reported that it consisted only of one positive peak that occurs around 30 msec post stimulus (Fifer & Sierra-Irizarry, 1988). Studies subsequent to Geisler have allowed defining and labeling of a series of peaks and troughs, which has become well known as AMLR waveform (Musiek, Geurkink, Weider, & Donnelly, 1984).

Several components of the AMLR waveforms are recognized in the literature known as No, Po, Na, Pa, Nb, Pb, and Pc (Musiek et al., 1984). However the AMLR Na, Pa, Nb, Pb, components are the most commonly recognized waveform:

1. No is a negative wave occurring at about 8-10 msec.
2. Po is positive vertex peak occurring within a range 11-13 msec.
3. Na is a negative wave occurring at about 15 msec.
4. Pa is positive vertex peak occurring within a range of 25 to 35 msec.
5. Nb is a negative wave occurring at about 40 msec.
6. Pb is positive peak occurring at latency range of 50 to 70 msec and is

often identified as P1 component of late auditory evoked potential (LAEP).

Among AMLR waves, the negative-positive Na/Pa complex is consistently obtained in normal subjects, between 16 and 30 msec after click stimulation (Deiber, Ibañez, Fischer, Perrin, & Mauguière, 1988).

Neurogenerators of AEPs

To understand the role of the auditory evoked potentials in assessment of central auditory functions, one must briefly consider the anatomy of the auditory pathway. It is also important to note that there is a significant signal processing at each nucleus level in the central auditory pathway. Inner hair cells in the cochlea transduce the mechanical energy of sound into electrical impulses in the auditory nerve. The auditory information from auditory nerve is processed in the ipsilateral dorsal /ventral cochlear nuclei. Afterward, the auditory impulses are projected bilaterally with a contralateral dominance to the superior olivary complex. Then the pathway continues up through the lateral lemniscus to the inferior colliculus, where partial decussation occurs. Further synapse activity occurs in the medial geniculate nucleus of the thalamus, before cortical processing in the primary auditory cortex on Heschl' s gyrus of the medial temporal lobe. Illustration of the anatomy of the auditory pathway and related AEPs generators are shown in Figure (2) adopted from(Kumar, Bhattacharya, & Makhija, 2000).

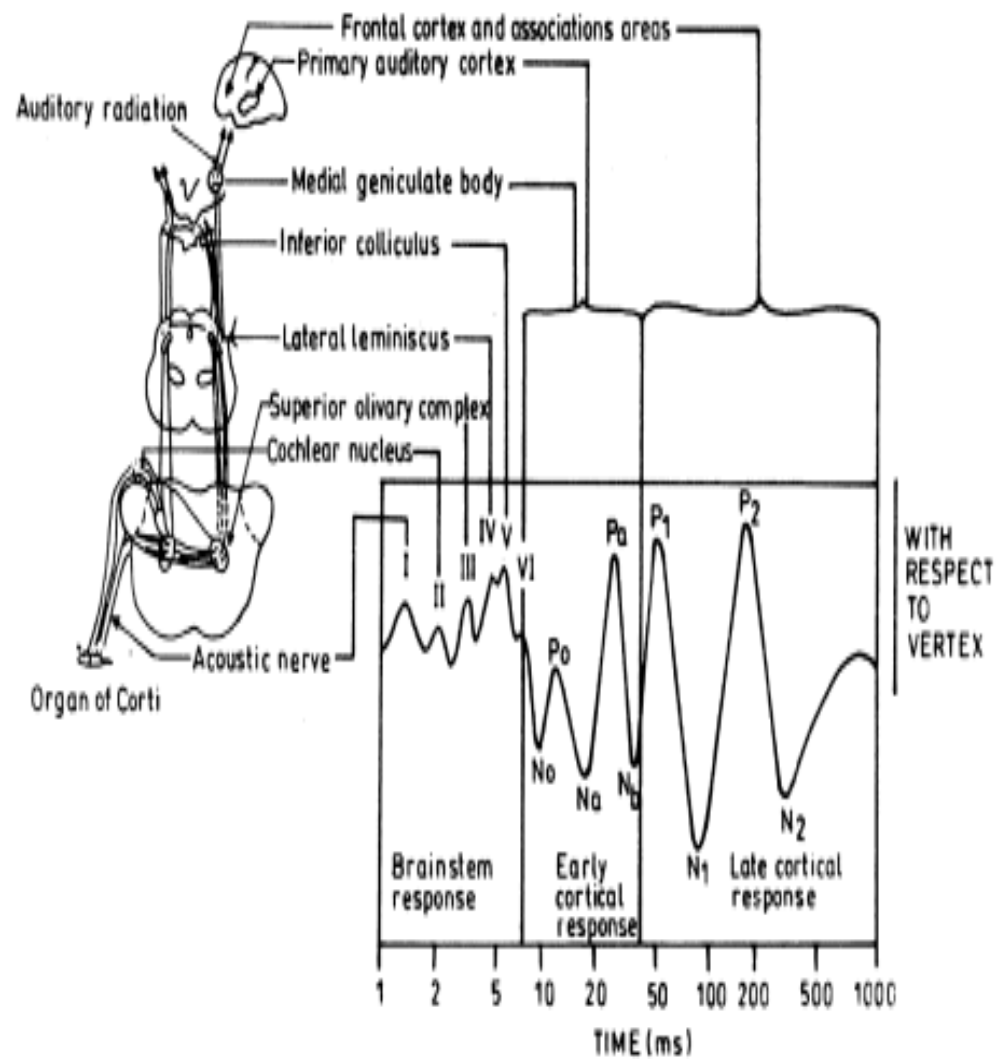


Figure 2. Neuroanatomical Correlates of AEPs.

Data from human investigations suggest that ABR positive peaks reflect compound activities from axonal pathways in the auditory brainstem (Hall, 2007). Generally, wave V is often the most common analyzed component of the ABR in clinical application and believed to represent activities generated in the lateral lemniscus fibers as they enter the inferior colliculus contralateral to the stimulated ear (Hall, 2007).

Subject Factors for ABR Waveform

Age. ABR matures at earlier age than later AEPs with most of the maturation changes in the ABR waveforms occurring in the first eighteen months of life; whereas, advanced age has minimal effect on the ABR waveform latency (Hall, 2007; Jerger & Hall, 1980).

Gender. Distinct effect of gender on ABR waves latency and amplitude has been reported for adult subjects (Jerger & Hall, 1980). Throughout adulthood and post-menopause, females show shorter latency and larger amplitude for ABR waves III, IV, V, and VI (Hall, 2007).

Body temperature. Normothermia of 37 degrees centigrade (C) or 98.6 Fahrenheit should be verified at the time of testing. Temperature exceeding 1 degree from this should be considered as a factor for the interpretation of the ABR outcome (Hall, 2007).

In general AMLR is generated by a complex system involving contributions and interactions of centers in the auditory pathway from midbrain to cortex (McGee et al., 1991). Both human and animal studies indicate that multiple brain areas contribute to the AMLR waveforms, and that likely contributors include auditory cortex, medial geniculate body, mesencephalic reticular formation and the inferior colliculus (Deiber et al., 1988; Kaga, Hink, Shinoda, & Suzuki, 1980; Kraus et al., 1982; Woods, Clayworth, Knight, Simpson, & Naeser, 1987).

The exact origins of the Pa component AMLR are not fully understood. Most of the evidence of the neurogenic origins of the AMLR waves are based on inferences from animal studies and studies of human subjects with anatomically defined cortical lesions (Fifer & Sierra-Irizarry, 1988). Evidence obtained from these human and animal investigations suggest that the Pa component is generated bilaterally within the primary auditory cortices (Deiber et al., 1988; Jacobson & Newman, 1990; Kaga et al., 1980; Kraus et al., 1982; McGee et al., 1991). However, Woods et al. (1987) and Kraus et al. (1982) have reported that patients who sustained bilateral temporal lobe infarctions remained physiologically capable of generating a Pa component. In fact, Woods et al. (1987) found no simple relationship between Na-Pa amplitude and the extent of damage to primary auditory cortex or auditory association areas. Thus, Woods and colleagues argue that combined damage to temporal lobe and the thalamo-cortical pathway are necessary to produce wave Pa abnormalities.

Thus, the intact Pa observed in some patients with bitemporal lobe lesions indicate the presence of an AMLR generating system outside the auditory pathway and suggest that Pa is generated from both cortical and subcortical structures (Woods et al, 1987). Furthermore, Jacobson and Newman (1990) provided evidence that Pa component in humans is composed of two functionally distinct generator systems: one is located in the temporal lobes bilaterally and the other one is a deep midline generator system that possibly resides within the mesencephalic reticular formation or polymodal thalamus. Both human and animal studies suggest that the inferior colliculus may contribute to the generation of Na wave (McGee et al., 1991).

Subject Factors for AMLR Waveform

Age. Early studies regarding obtaining reliable AMLR waveforms in infants and young children provided controversial results. Engel (1971) reported that AMLR response to clicks were unstable or absent in the majority of 24 neonates and repeatable only in 3 of the 24 newborns tested during sleep. Similarly, Kraus, Smith, Reed, Stein, & Cartee (1985) reported absent AMLR waveform in neurologically normal children under the age of 10 years when tested in a sleep or sedated conditions. These results contradict the results of Mendel, Adkinson, & Harker (1977) which revealed that AMLR could be elicited from neonates. In this study Mendel and colleagues obtained AMLR waves from 18 normal infants divided into three groups 1, 4, 8 months of age. Similarly, Tucker & Ruth (1996)

reported that the prevalence of AMLRs in their study groups was 70 to 100 percent for subjects ranging in age from 2 days to 35 years.

At the other end of the human age range, AMLR has been reported to be larger in amplitude above the age of 60 years (Picton, 2011). The possible explanation for increased amplitude in an older population might be age-related decline in the inhibitory circuit within the auditory system that is mediated by gamma-aminobutyric acid (Gerken, Hesse, & Wiorkowski, 2001; Picton, 2011).

Gender. Tucker, Dietrich, Harris, and Pelletier (2002) reported a significant effect of gender on Pa latency and Pa amplitude. In this study, Tucker and colleagues examined AMLR waveforms in 20 young adult male and female subjects using four different repetition rates. The results of Tucker et al. (2002) revealed longer Pa latencies in male subjects, and larger Pa amplitudes in female subjects. Gender did not have a significant effect on the Pb waveform (Tucker et al., 2002).

Race. There is paucity in the literature on the effect of race on the AMLR waveforms.

Stimulus ear. Cacace, Satya-Murti, and Wolpaw (1990) noted that Pa component of the AMLR was prominent with both monaural and binaural stimulation, whereas the Pb component was more reliably recorded with right ear or binaural stimulation.

State of arousal. The latency of AMLR waveforms are resistant to the effect of sleep; however, the amplitude varies depending on the stage of sleep

(Fifer & Sierra-Irizarry, 1988). Deiber and colleagues (1989) noted significant variation in AMLR waves Na and Pa latency and amplitude at different sleep stages (stage II to stage IV). The findings of Deiber et al. (1989) demonstrate that the responsiveness of the auditory cortex to acoustic stimuli is modulated during sleep and highlighted the importance of monitoring vigilance during AMLR recordings.

In general, AMLR Na and Pa waves remain clearly recognizable with sleep; however, the amplitudes are smaller and the latencies are longer especially in the deeper stages of sleep (Picton, 2011). Conversely, Nb and Pb components often become unrecognizable in stages III and IV of sleep (Picton, 2011).

AEPs and Tinnitus

The non-invasive nature of AEPs and their ability to evaluate the integrity of the central auditory system make them an appealing measure to detect changes in neural activity within the central auditory system associated with tinnitus. Several studies investigated the potential use of auditory evoked potentials as an objective measure to detect changes in neural activity associated with tinnitus. However, the results from these studies were conflicting.

Gerken et al. (2001) investigated the use of AMLR in individuals with tinnitus. In this study, Gerken and colleagues grouped their participants into four categories: 1) tinnitus group (n=9) with a mean age 45.7 years; 2) normal hearing without tinnitus group (n=11) with a mean age 28 years; 3) hearing loss without

tinnitus group (n=8) with a mean age 40.9 years; 4) elderly without tinnitus group (n=7) with a mean age 63.6 years. Gerken and colleagues (2001) reported no significant differences between groups in the AMLR results. However, further analysis on the AMLR data in the problem-tinnitus group showed enhanced AMLR amplitudes in 5 of 9 individuals (59%) in this group. Gerken et al. (2001) suggested that tinnitus subtypes might exist and could be responsible for the enhanced AMLR amplitudes found in certain individuals within this group.

Based on the results of Gerken et al, (2001) Theodoroff, Chambers, and McMillan (2011) conducted a follow-up study that focused mainly on patients with severely debilitating tinnitus. The main purpose of the study was to examine the effect of tinnitus severity on AMLR amplitude. The results of this study revealed that severe tinnitus alone does not comprise a homogeneous group of individuals and highlighted the importance of considering the diversity of etiologies associated with tinnitus.

The variability reported in AEPs results in individuals with tinnitus may be related to various neurophysiological models or mechanisms of tinnitus perception that result in alteration of the neural signal processing. Another possible explanation is that the variability in AEPs waveforms is not related to the variability of tinnitus mechanisms, but related to other factors that are associated with tinnitus such as hearing loss and aging.

Since various tinnitus etiologies can have different effects on the individual structures along the auditory pathway, it is important to consider the homogeneity

of tinnitus etiology among tinnitus subjects. Dos Santos Filha, Samelli, & Matas (2015) examined the changes in AMLR among a homogenous population with regard to the cause of tinnitus.

Sixty normal hearing subjects with occupational noise exposure (above 85 dB A) with and without tinnitus participated in this study. However, Dos Santos Filha et al. (2015) did not specify the duration of the noise exposure for the participants in their study. The results showed some alteration of the AMLR in the form of increased Na/Pa amplitude and latency in the tinnitus group compared to the control group. Although this variation in the AMLR waveform did not reach the statistically significant levels, these findings suggest that a modification of transmission of neural impulses along the auditory pathways in cortical and subcortical regions is present in tinnitus subjects.

Singh, Munjal, and Panda (2011) investigated the use of AEPs (AMLR and ABR) as an objective measure for the changes in central auditory system in normal hearing subjects with and without tinnitus. They hypothesized that alteration of the outer hair cell function and the associated changes in central and subcortical functions is the cause for tinnitus without hearing loss. Forty-five normal hearing subjects participated in this study; twenty-five with tinnitus and twenty without tinnitus. The results revealed changes in function of the middle latency response generators in the form of increased Na/Pa amplitudes in the tinnitus group, compared with control subjects. ABR results showed prolongation

of wave I latency and shortening of wave V latency, wave III–V and I–V inter-peak latencies in the tinnitus ears of the study group, compared with controls.

Similarly, Nemati et al. (2014) investigated the role of peripheral and central auditory system in tinnitus generation in normal hearing subjects with and without tinnitus. Results demonstrated differences in ABR waves amplitude between the tinnitus and control groups. The amplitude of the wave I was slightly smaller, and the amplitude of wave V was slightly larger in the tinnitus group, although the difference was not statistically significant. However, comparing the V/I amplitude ratio in the groups showed that it was significantly larger in the tinnitus group. Nemati et al. (2014) provided several justifications of the reduction of wave I amplitude in the tinnitus group with normal hearing. First, Wave I amplitude reduction may result from loss of higher threshold auditory nerve fibers that has no effect on hearing thresholds. Another possible explanation for this finding is the existence of sporadic damage to the inner hair cells that does not cause hearing loss, but leads to reduction of the amplitude of wave I. Increased spontaneous neural activity at higher levels of the auditory pathways, including dorsal and ventral cochlear nuclei and inferior colliculus, are among the theories about the origin of the tinnitus. Thus, changes in the ABR waves amplitude indicate increased spontaneous activity of neurons of the brainstem auditory centers (Nemati et al., 2014).

Auditory deprivation is one of the tinnitus models that can alter the excitatory-inhibitory balance in the central auditory system. Subsequently, this

excitatory-inhibitory imbalance can result in changes of the neuronal activity in different parts of the auditory pathway including the dorsal cochlear nucleus, inferior colliculus, thalamus and/or auditory cortex. With these areas contributing to the generation of AEPs waveforms, it can be hypothesized that AEPs would be a promising tool to detect any changes in the neuronal activities in these areas.

Thus, the main purpose of the current study was to examine the central auditory processing changes resulting from auditory deprivation due to silence exposure and subsequent temporary tinnitus perception, objectively using AEPs (ABR and AMLR).

Purpose of the Current Research

To date, the exact mechanisms of tinnitus generation are still not fully understood. Despite the presence of several proposed causes and hypothesis for tinnitus generation, none of these theories is exclusive. A few studies have investigated the effect of auditory deprivation as a result of silence exposure on tinnitus perception. The results of these studies revealed a high prevalence of perception of tinnitus-like sounds during silence and demonstrated that directed auditory attention plays an important role while auditory suggestion have a minor role in these perceptions. To the author's knowledge, no studies have examined the central auditory nervous system changes with regard to silence-induced tinnitus perceptions using AEPs. AEPs provide a mean to examine the possible changes along the auditory pathway associated with this tinnitus-like perception

as well as highlighting any possible difference between groups (tinnitus and non-tinnitus groups) with regard to auditory activities, in the absence of other pathologies that can affect different structures along the auditory pathway.

Research Hypotheses

It was hypothesized that:

1. Auditory deprivation as a result of silence exposure will result in tinnitus-like perception in most of the participants even though this study controlled for directed auditory attention.
2. There will be significant increase in the AMLR Pa-Na wave amplitude and decrease in the AMLR Pa-Na wave latency in ipsilateral and contralateral conditions after auditory deprivation due to silence exposure. Also, There will be significant increase in the ABR wave V amplitude and decrease in the ABR wave V latency in ipsilateral and contralateral conditions after auditory deprivation due to silence exposure.
3. There will be significant difference in AMLR Pa-Na wave amplitude and latency as a result of tinnitus experience. AMLR Pa-Na wave amplitude will be larger and the latency will be shorter in subjects who experience tinnitus-like perceptions after auditory deprivation due to silence exposure than those who do not have tinnitus-like perceptions. Also, there will be significant difference in ABR wave V latency and amplitude as a result of tinnitus experience.

4. There will be difference in central auditory activities between those who perceive tinnitus-like sounds during silence (tinnitus group) and those who do not perceive tinnitus during silence (non-tinnitus group) as measured by amplitude of AEPs (ABR and AMLR). AMLR Na/Pa and ABR wave V amplitudes will be higher in tinnitus groups than non-tinnitus group, which reflect more activities within the central auditory pathway that can be detected as tinnitus in the absence of masking environmental sounds during silence.

Research Questions

1. Will exposure to silence result in perception of tinnitus-like sounds in normal hearing individuals?
2. Will auditory deprivation as a result of silence exposure change the central auditory processing functions as measured by AMLR Pa-Na and ABR wave V amplitude and latency?
3. Will experiencing tinnitus after auditory deprivation due to silence exposure have an impact on the central auditory processing functions measured by AMLR Pa-Na wave amplitude and latency and ABR wave V amplitude and latency?
4. Will tinnitus and non-tinnitus groups differ in central auditory activities as measured by AMLR Na/Pa and ABR wave V amplitudes?

CHAPTER III

METHODS

Institutional Review Board (IRB) approval was obtained from the University of North Carolina at Greensboro (UNC-G) for this study.

Participants

The subject pool of this study consisted of 60 normal hearing adult females. No male subjects participated in this study in order to control for gender effect on AEPs measures and to prevent any possible variations of waveforms that can result from gender difference (Hall, 2007). Additionally, the findings of Tucker et al., (2005) revealed no gender effect on the emergence of tinnitus after silence experience. Race was not considered to be an exclusionary factor in the present study. The age of the study participants ranged between 18 and 40 years to control for the age effect on the AEPs measurements and tinnitus perception. The subjects' health conditions were assessed using a general health questionnaire that documented prior history of chronic medical conditions such as hypertension and diabetes as well as history of ear infections and surgeries etc.

Inclusion criteria. All subjects included in this study were adult females between 18 and 40 years old. The following criteria were essential for participation in this study to ensure normal peripheral hearing:

1. No history of head trauma, neurological disease, or ear surgery.
2. Normal outer ear and tympanic membrane determined by otoscopic examination
3. Normal bilateral middle ear function determined by type (A) tympanogram with peak pressure between -100 to +100 daPa.
4. Normal bilateral hearing sensitivity determined by pure tone threshold better than 25 dB HL for octave frequencies between 250 and 8000 Hz.

Exclusion criteria. Subjects were excluded from the study if they were younger than 18 or older than 40 years of age. Subjects were excluded if they had perforated tympanic membrane or abnormal middle ear function, which indicated the presence of a minimal conductive hearing loss. Subjects were excluded if they had elevated hearing thresholds as indicated by the results of the audiometry. Furthermore, subjects were excluded if they were prescribed or currently taking any medications for depression, anxiety, stress, bipolar disorder, schizophrenia, or insomnia.

Materials

General health data was obtained using a General Health Questionnaire. During the lab visit, the primary investigator emailed the link for a Qualtrics generated General Health Questionnaire and instructed participants to complete it. Within the same visit, behavioral audiometric measures, silence experience, and AEPs measures were obtained. At the end of the visit, each subject completed another Qualtrics generated survey about possible sounds they might have perceived during the silence period using a Silence Questionnaire.

Instrumentation and Equipment

Behavioral testing: Questionnaires. Two Qualtrics generated questionnaires were administered in this study. All study participants completed both questionnaires:

1. General Health Questionnaire
2. Silence Questionnaire

Audiometric testing. All subjects were administered the same hearing tests, which included otoscopy, tympanometry, and audiometry in order to determine their hearing sensitivity and middle ear function.

1. Otoscopy: A handheld otoscope (Welch Allyn) was used to examine each subject's ear prior to the hearing testing. This test evaluates the external auditory canal and the tympanic membrane.
2. Tympanometry: GSI TympStar Middle Ear Analyzer used to obtain tympanometric peak pressure. A soft-tip probe was placed inside the ear

canal to create a seal, and the GSI TympStar Middle Ear Analyzer then automatically measures middle ear pressure and compliance.

3. Audiometry: A Grayson-Stadler (GSI) 61 Clinical Audiometer and ER-3A insert transducer was used to determine the hearing sensitivity in the frequency range of 250 to 8000 Hz. Subjects sat in the sound treated room and were given a response button to press when they heard the presented tone at different frequencies in order to determine hearing thresholds.
4. Intelligent hearing system Smart EP was used to gather and amplify the AEPs data. Procedures are described in more detail below.

Stimuli. AEPs were elicited using monaural rarefaction click stimuli presented through the Intelligent hearing systems Smart EP to the tip-trode at 75 dB nHL at signal rates of 7.1/second. Scalp EEG activity were amplified 100,000 times and filtered with 10- 1500 Hz filter. The scalp EEG activities were averaged over a 50 – msec time base. The raw EEG and evoked responses data were stored on computer for post hoc analysis. Ipsilateral and contralateral AEPs responses were recorded to right ear stimuli. The choice of the right ear stimulation was based on the fact that 80% of the central auditory pathway cross to the opposite hemisphere and is processed in the left hemisphere. The choice of the right ear stimulation was also based on the results of previous studies that showed no ear effect on the Na, Pa components of AMLR measurements

especially in young adults and middle age group (Hall, 2007; Tucker, Dietrich, McPherson, & Salamat, 2001; Weihing & Musiek, 2014).

Procedures

Recruitment procedure. Subjects were recruited through word of mouth, email, and flyers distributed by the principal investigator. Upon arrival at the lab, where the experiment's procedures were administered, the consent form was explained to the subjects. A signed copy of the consent form was given to the subject and a second copy kept in the subject's de-identified file. All testing took place at the University of North Carolina at Greensboro's Neuro Lab located on the third floor of the Ferguson building. All paper copies of test forms, including the experiment consent forms; were securely kept in a locked file cabinet. All information obtained in this study is strictly confidential unless law requires disclosure.

Test protocol. All the testing procedures for this study were completed in a sound attenuating room that met the criteria for permissible ambient noise for audiologic testing.

Once each subject arrived in the Neuro Lab, each subject received a brief oral description of the study and signed a consent form. During oral presentation and on each subject's response forms, the word "tinnitus" was not used, so the subject's perceptions and responses would not be biased.

Each subject was evaluated through otoscopic examination, middle ear examination, and peripheral hearing threshold, in order to determine the

fulfillment of the inclusive criteria of the study. Once normal hearing was determined, the subject was prepared for the AEPs (AMLR and ABR) measurements.

First AEPs measurements. Intelligent hearing system Smart EP was used to generate the click stimulus and to acquire the evoked responses. Each subject was seated in a recliner chair and asked to relax and keep awake. The principal investigator made sure that the subjects remained awake during testing and remained in the room with them during testing. Skin surfaces for the electrode sites on the subject's scalp and forehead were cleaned with an alcohol pad to remove excess oil or make up at the intended electrode placement locations. Then, the electrode sites were rubbed with mild abrasive solution and then with a normal saline solution to improve the electrode impedance. Gold cup reusable electrodes were filled with conductive gel and secured in place using a small piece of surgical tape. Per manufacture recommendation, a small piece of gauze was placed between the electrode and the surgical tape. Two-channel recordings (ipsilateral and contralateral) were obtained for each AEP (AMLR and ABR) waveform. A total of 2000 sweeps (2 x 1000) were recorded in each condition (pre-silence and pos-silence).

The electrodes were placed on the following locations: 1) non-inverting electrode on the vertex (Cz); 2) inverting electrodes in the right ear canal (A2) using tip-trode and on left ear lobe (A1); and 3) ground electrode on the forehead (Fpz). Measured electrode impedance were kept below 5000 ohm and balanced

to 1500 ohms between electrode pairs. After impedance verification across the electrodes, each subject was presented with rarefaction click stimuli through tip-trode insert transducer in the right ear (Fig 3). The computer recorded the electrophysiological results emitted by the electrodes.

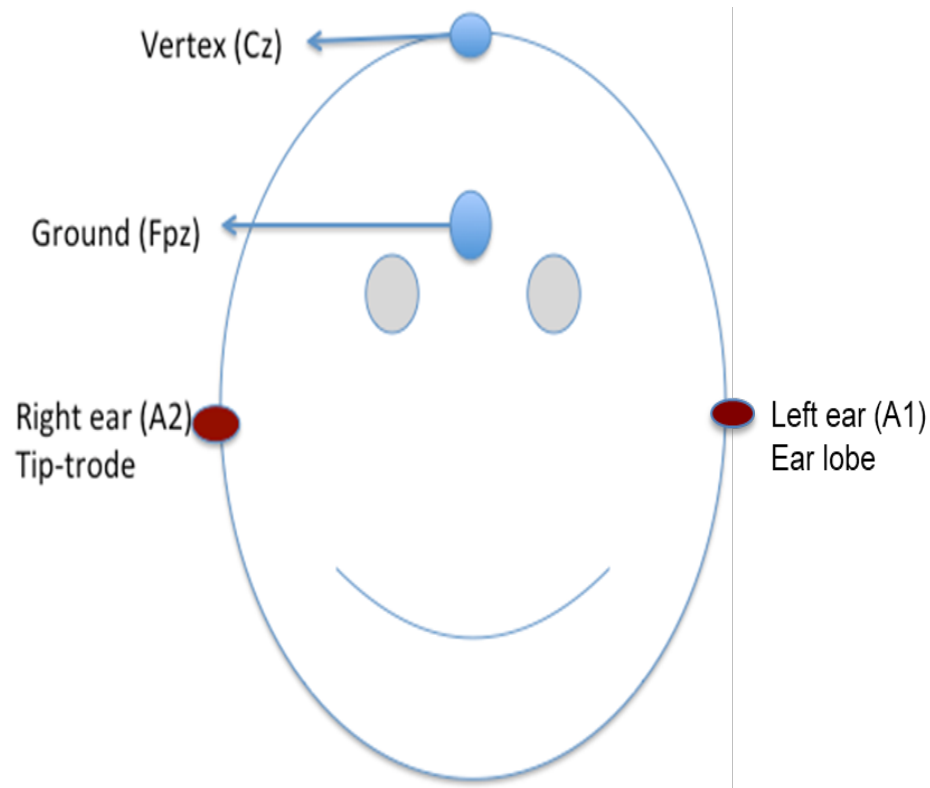


Figure 3. Electrode Montage used for AEPs Measurements

Silence experience. After the first AEPs (ABR and AMLR) measures were obtained, each subject was seated in the sound booth alone for ten minutes. This time frame was based on the results of the earlier studies on silence, which demonstrated emergence of auditory perception in the majority of their participants within 5 minutes of the silence experience (Del Bo et al., 2008; Heller & Bergman, 1953; Knobel & Sanchez, 2008; Tucker et al., 2005). Each subject was given verbal instructions for the listening experiment, the primary investigator tried to control for the effect of directed auditory attention by stating that the study was about the effect of silence on the auditory system. In the pre-test instructions, the primary investigator informed the subjects that they would complete a short questionnaire about any possible sensory perception during the silence experience at the end of the experiment. The verbal instructions were as follows: “In this study we are looking for the effect of silence on the auditory system, so you will sit in silence in this room for ten minutes. During this time you need to be relaxed and awake. At the end of the experiment you will complete a short questionnaire about the silence period”.

Second AEPs measurements. Immediately following the silence exposure for ten minutes, the second AEPs (ABR and AMLR) recording were obtained using the same protocol utilized to obtain the first measurements. Then, the electrodes were removed and the electrode locations were cleaned.

Following the second recording, each subject was asked to complete an online questionnaire that documented any sounds heard during the silence

experience. On the survey, common sounds that were listed include buzz, roar, heartbeat, whistling, hum, running water, pulse, hiss, ring, crickets, whizzing, no sound, and other. Additional questions were provided on the survey to allow the subjects to further record their experience. These questions included the time and site of perception of the tinnitus-like sounds. The test procedure for this study lasted at least 90 minutes. Figure (4) provides schematic diagram for the study procedure.

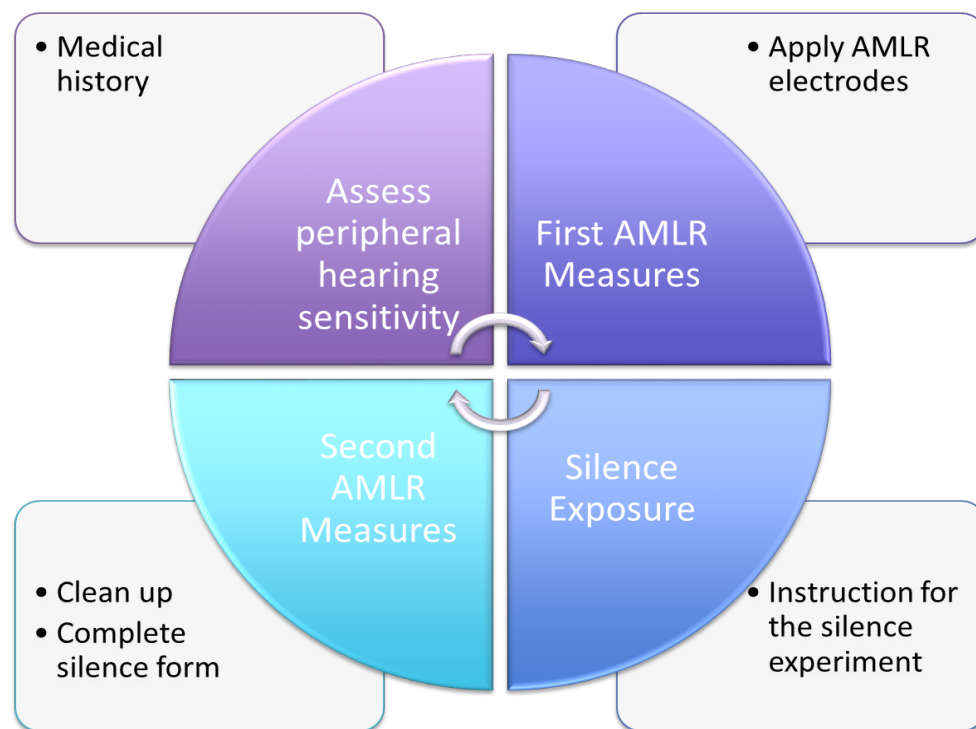


Figure 4. Illustrations of the Study Procedures

Statistical Designs and Analysis

Peak to peak amplitudes (μV) and absolute latencies (msec) of the AMLR Na /Pa waveform and ABR wave V measures for each subject were entered into an SPSS data spreadsheet along with each subject's demographics, audiometric test results, General Health Questionnaire responses, and Silence Questionnaire responses. Means, standard deviations, and ranges were calculated for amplitude and latency of ABR wave V and AMLR Na/Pa waves.

Peak amplitude of the AMLR Na/Pa waveform was measured from the bottom of the preceding Na trough to the highest point on the Pa waveform. Latencies of Na and Pa waves were measured to the highest point on the Pa waveform and to trough of Na waveform (Fig 5). Peak amplitude of ABR wave V was measured from the highest point to the following trough. Descriptive and inferential statistics were used to analyze the data. Peak amplitude and latency of Na/Pa waves and ABR wave V for ipsilateral and contralateral conditions were evaluated using a repeated measures analysis of variance (ANOVA). In this study, the alpha level was set at 0.05, with a 95% confidence interval in all statistical calculations.

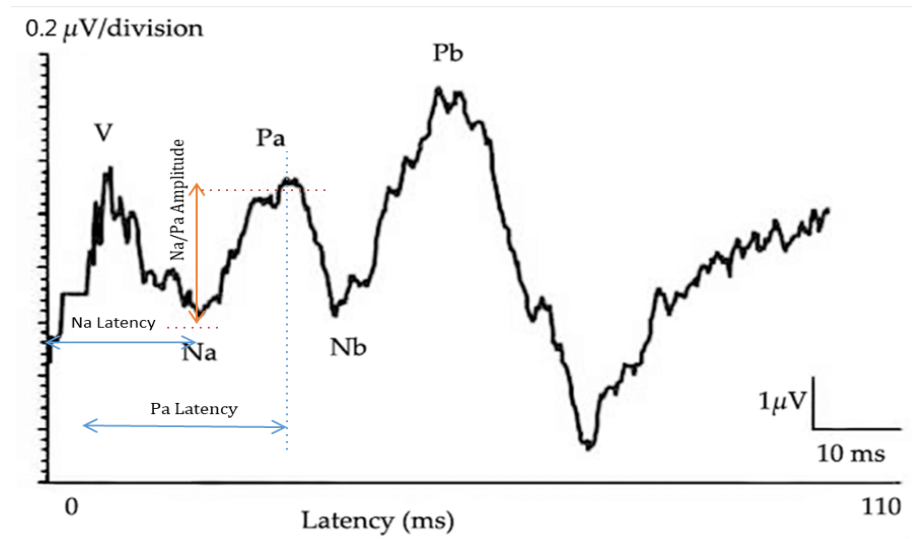


Figure 5. Illustrations of the AMLR Na/Pa Latency and Amplitude Measurements

The following statistical analyses were used to answer the following questions:

RQ 1: Will auditory deprivation as a result of silence exposure result in tinnitus-like perception, while controlling for directed auditory attention?

Responses for question on the Silence Questionnaire regarding whether or not the subject perceived tinnitus-like sounds during silence as well as responses for the description of any tinnitus perception during silence such as tinnitus onset, location, number of tinnitus sounds heard, and log of different sounds perceived were entered to SPSS spread sheet. Descriptive statistical analysis were performed to report number and percentage of subjects perceive tinnitus-like sounds during silence as well as information with regard tinnitus location, onset time, and the nature of perceived tinnitus-like sounds perceived by the subjects.

RQ 2: Will auditory deprivation as a result of silence exposure change the central auditory processing functions as measured by wave amplitude and latency recorded using auditory evoked potentials (ABR and AMLR)?

To assess the hypothesis that the central auditory processing functions were altered as a result of silence, repeated measures ANOVA was used to examine any differences between pre and post silence exposure measurements for AMLR waves (Na and Pa) amplitude and latency for both ipsilateral and contralateral conditions as well as ABR wave V amplitude and latency for both ipsilateral and contralateral conditions.

RQ 3: Will experiencing tinnitus during silence exposure have an impact the central auditory processing functions measured by wave amplitude and latency recorded using auditory middle latency response and auditory brainstem response?

Assessment of overall differences were used to examine the hypothesis that tinnitus perception will alter the central auditory processing functions measured by wave amplitude and latency recorded using auditory middle latency response and auditory brainstem response.

Repeated measures ANOVA was used to examine any evidence regarding pre and post silence exposure AMLR waves (Na and Pa) amplitude and latency differences as well as ABR wave V amplitude and latency for those who perceived tinnitus and those who did not perceive tinnitus during silence exposure.

RQ 4: Will tinnitus and non-tinnitus groups differ in central auditory activities as measured by AMLR Na/Pa and ABR wave V amplitudes?

To assess the hypothesis that level of brain activities will be different between groups with regard to tinnitus perception, repeated measures ANOVA was used to examine any group differences with regard to tinnitus perception for AMLR Na/Pa as well as ABR wave V amplitude and latency for both ipsilateral and contralateral conditions.

CHAPTER IV

RESULTS

General Descriptive and Behavioral Data

General demographic data about the subjects' age, noise exposure, and general health condition that determined their eligibility to participate in the study was obtained using a General Health Questionnaire. Subjects' self-reported data about tinnitus perception, location, time of onset during silence, number and nature of different sounds perceived during silence was obtained from each subject using a Silence Questionnaire.

Table 1 shows the general demographic data obtained from a total of 60 female subjects who participated in this study including age, pure-tone averages of all tested frequencies for right and left ears, and tinnitus-like perceptions. The age of the study subjects ranged from 18 to 40 years with a mean of 24.2 years and SD= 5.968.

During the brief period of silence exposure, thirty-three out of sixty subjects (55%) reported perceiving at least one tinnitus-like sound. The mean age for the group who perceived tinnitus-like sounds during silence exposure (Tinnitus group) was 23.82 years and SD= 6.187, while the mean age for the group who did not perceive tinnitus during the silence period (non-tinnitus group)

was 24.67 and SD=5.771. A one-way ANOVA testing revealed that age was not significantly different between the two groups ($F_{1,10.7} = 0.297, \rho = 0.588$).

Table 1

General Demographics

Characteristic		Tinnitus	Non tinnitus	P-Value
Age	M	23.82	24.67	0.59
	SD	6.19	1.08	
PTA/right ear	M	6.09	6.33	0.73
	SD	2.35	2.95	
PTA/left ear	M	6.54	6.17	0.63
	SD	2.75	3.14	
Tinnitus	N	33	27	
perception	Percent	55%	45%	

M= Mean, SD=Standard Deviation

All subjects who participated in this study had normal hearing thresholds of 25 dB HL or less. All subjects' pure-tone averages (PTA) were calculated for the right ear (M=6.19, SD= 2.62) and left ear (M= 6.38 SD= 2.9).

In tinnitus group, the mean pure tone average for the right ear is 6.086, SD= 2.35, left ear is 6.54, SD= 2.75. While for the non-tinnitus group, the mean pure tone average for the right ear is 6.33, SD= 2.95, left ear is 6.17, SD= 3.14.

A one-way ANOVA was also computed comparing the PTA across the two groups. There was no statistical difference between the mean PTA of the two groups for either the right or the left ear ($RE: F_{1,0.87} = 0.124, \rho = 0.726$; $LE: F_{1,2} = 0.234, \rho = 0.631$).

Figure 6 illustrates the right ear audiometric mean thresholds for the two groups (Those who perceived tinnitus during silence and those who did not perceive tinnitus). Both groups has right ear normal hearing threshold below 10 dB HL. The mean threshold for the non-tinnitus subjects was slightly higher than that for tinnitus subjects at 8000 Hz, but this difference was not statistically significant.

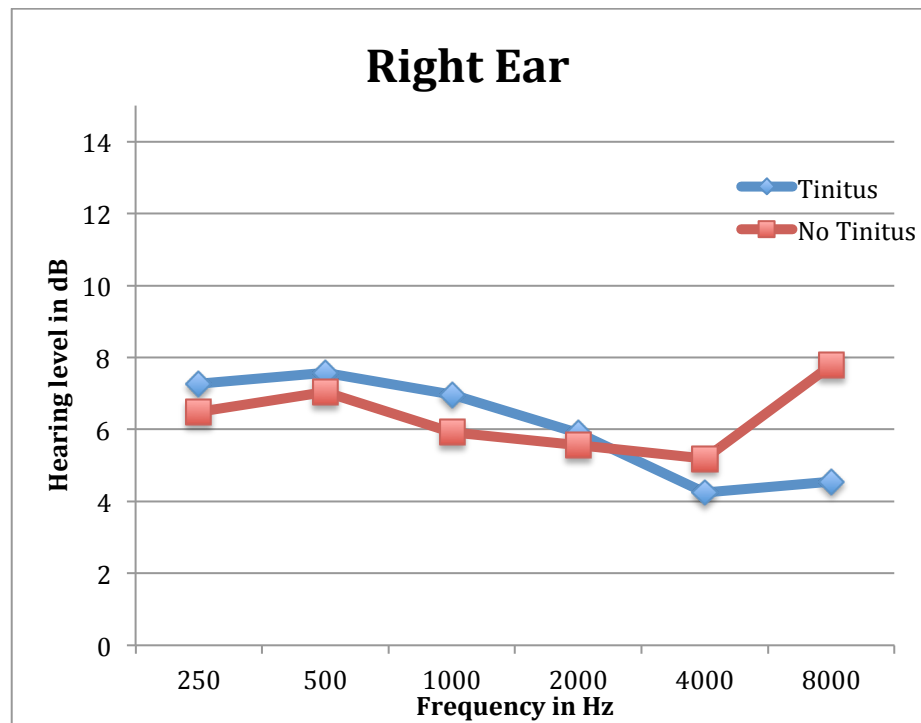


Figure 6. Right Ear Mean Thresholds for Tinnitus and Non-Tinnitus Groups

Figure 7 illustrates the mean audiometric thresholds left ear for those who perceived tinnitus during silence and those who did not perceive tinnitus. Similarly, both groups had left ear normal hearing threshold better than 10 dB HL. The mean threshold for the non-tinnitus subject was slightly higher than that for tinnitus subjects at 8000 Hz, but still this difference was insignificant.

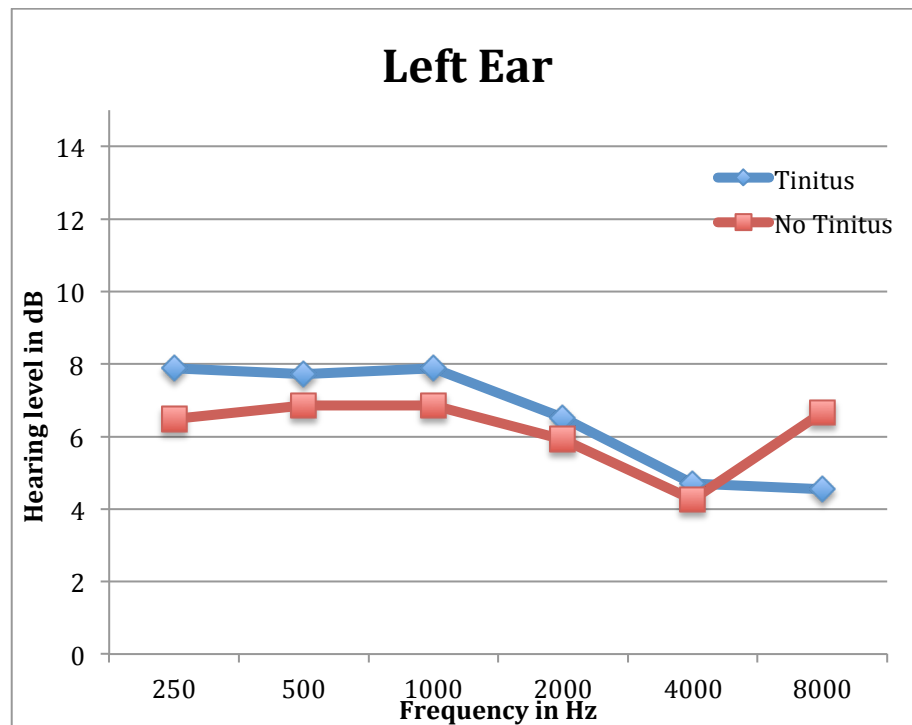


Figure 7. Left Ear Mean Thresholds for Tinnitus and Non-Tinnitus Groups

Table 2 shows the number of auditory sounds perceived by the subjects during the silence exposure. The majority of subjects in the tinnitus group perceived either one (20%) or two sounds (20%). While (12%) perceived three sounds, only one subject perceived four sounds, and another subject perceived five sounds.

Table 2

Frequency of Auditory Sounds Perceptions

Number of auditory perceptions	Frequency	Percent
0	27	45%
1	12	20%
2	12	20%
3	7	11.7%
4	1	1.7%
5	1	1.7%
Total	60	100%

Table 3 represents the frequency and percentage of the onset and location of tinnitus-like sounds perceived during silence in the total sample participated in the study. The majority of the subjects who perceived tinnitus-like sounds reported that those perceptions occurred within the first five minutes of the silence exposure. The table shows that three subjects reported perceiving tinnitus-like sounds immediately during silence exposure. Thirteen subjects perceived tinnitus-like sounds within the first two minutes, and remaining seventeen subjects perceived tinnitus-like sounds within five minutes of the ten minutes of silence exposure.

Table 3

Tinnitus Onset and Location

T. Onset	Frequency	Percent	T. Location	Frequency	Percent
Immediately	3	9.1%	Left ear	8	24.2%
Within 2 min.	13	39.4%	Right ear	6	18.2%
Within 5 min.	17	51.5%	Both ears	9	27.3%
At 10 min.	0	0%	Head	10	30.3%
Total Tinnitus	33	55%	Total	33	55%

Table 4 shows the types of tinnitus-like sounds perceived by the subjects when they were sitting in a relatively silent environment for a short period of time (10 minutes). Pulse (39%), other (39%), heartbeat (36%), hum (30%), buzz (27%), and roar (12%) were the most common sounds perceived during the silence period. Noting that the majority of the subjects in the current study reporting hearing more than one sound. Of the thirty-three subjects reported tinnitus perception, eight subjects heard solely heartbeat or pulse sounds, while the remaining subjects (25 subjects) heard at least one tinnitus sound other than pulse or heartbeat.

Table 4

Types of Tinnitus Sounds Heard by Subjects During Silence

Type	Sound	Number	Percent
Auditory perceptions	Other	13	39%
	Hum	10	30%
	Buzz	9	27%
	Roar	4	12%
	Crickets	2	6%
	Ringings	1	3%
	Hiss	1	3%
	Whistling	1	3%
	Whizzing	1	3%
	Running water	0	0%
Pulsatile	Pulse	13	39%
	Heartbeat	12	36%

Physiological Data Analysis

Auditory evoked potentials waveforms including ABR wave V and AMLR Na/Pa waves latencies and amplitude obtained before and after silence exposure for both ipsilateral and contralateral conditions for each subject were analyzed using repeated measures ANOVA to examine any possible changes along the

central auditory pathway as a result of silence experience as well as the overall group difference as a result of tinnitus perception.

ABR Wave V Analysis

Table 5 shows the mean and the standard deviations of the ipsilateral ABR wave V latency and amplitude for pre-silence and post-silence recordings for both tinnitus and non-tinnitus groups. The mean latency for the ipsilateral ABR wave V for tinnitus group was about 5.78 ms and 5.8 ms for pre-silence and post-silence recordings respectively. Ipsilateral ABR wave V mean latency for non-tinnitus groups was 5.7 and 5.78 for pre-silence and post-silence recordings. The mean amplitude for the ipsilateral ABR wave V for the tinnitus group was about 0.56 μ A and 0.51 μ A for pre-silence and post-silence recordings. The mean of the ipsilateral ABR wave V amplitude for the non-tinnitus group was about 0.57 μ A and 0.56 μ A for pre-silence and post-silence recordings.

Table 5

Ipsilateral Mean ABR Wave V Latency and Amplitude

Parameter	Pre-silence		Post-silence	
	Tinnitus	No Tinnitus	Tinnitus	No Tinnitus
	Mean	Mean	Mean	Mean
	SD	SD	SD	SD
Wave V Latency (ms)	5.78	5.77	5.8	5.78
	0.19	0.23	0.21	0.22
Wave V Ampl ((μ A)	0.56	0.57	0.51	0.56
	0.26	0.2	0.2	0.21
SD= standard deviation; Ampl = Amplitude				

Table 6 shows the mean and the standard deviations of the contralateral ABR wave V latency and amplitude for pre-silence and post-silence recordings for both tinnitus and non-tinnitus groups. The mean latency for the contralateral ABR wave V about 5.92 ms and 5.95 ms for tinnitus group in pre-silence and post-silence recordings respectively. Mean contralateral ABR wave V latency for non-tinnitus group was about 5.91 ms and 5.94 ms in pre-silence and post-silence recordings respectively. Both groups showed minimal increase in the mean latency for post-silence than the pre-silence ABR wave V latency.

The mean amplitude for the contralateral ABR wave V was about 0.41 μ A and 0.42 μ A for tinnitus group in pre-silence and post-silence recordings

respectively. Mean contralateral ABR wave V amplitude was about 0.39 μA and 0.43 μA for non-tinnitus group in pre-silence and post-silence recordings respectively.

Table 6

Contralateral Mean ABR Wave V Latency and Amplitude

Parameter	Pre-silence		Post-silence	
	Tinnitus	No Tinnitus	Tinnitus	No Tinnitus
	Mean	Mean	Mean	Mean
	SD	SD	SD	SD
Wave V Latency (ms)	5.92	5.91	5.95	5.94
	0.26	0.26	0.28	0.27
Wave V Ampl ((μA))	0.41	0.39	0.40	0.43
	0.22	0.17	0.22	0.22

SD= standard deviation; Ampl = Amplitude

Effect of Silence on ABR Wave V

In order to examine the changes on the central auditory nervous system as a result of a brief period of silence, Within Subjects' effects on ABR wave V latency and amplitude before and after silence exposure were analyzed for ipsilateral and contralateral recordings utilizing ANOVA.

Table 7 shows the results of ANOVA analysis of the ipsilateral ABR wave V latency and amplitude. Within subject effect of silence on the Ipsilateral ABR

wave V latency and amplitude revealed no statistical significant effect of silence on ABR wave V latency ($F = 2.98$, $p = 0.09$), nor amplitude ($F = 2.65$, $p = 0.11$). Also, there was no interaction effect of silence and tinnitus for both latency ($F = 0.64$, $p = 0.43$) and amplitude ($F = 1.13$, $p = 0.29$).

Table 7

Within Subjects Effect of Silence for Ipsilateral ABR Measures

Measure	Source	F	Partial η^2	P (Sig)
Wave V Latency	Silence	2.98	0.049	0.09
	Silence* Tinnitus	0.64	0.011	0.43
Wave V Amplitude	Silence	2.65	0.044	0.11
	Silence* Tinnitus	1.13	0.019	0.29

Table 8 shows the results of ANOVA analysis of the contralateral AMLR wave V latency and amplitude. Within subject effect of silence on the contralateral ABR wave V latency and amplitude revealed a significant effect of silence on ABR wave V latency ($F = 4.5$, $p = 0.03$) and no significant effect on wave V amplitude ($F = 0.4$, $p = 0.52$). There was no interaction effect of silence and tinnitus for both latency ($F = 0.008$, $p = 0.9$) and amplitude ($F = 1.6$, $p = 0.22$).

Table 8

Within Subjects Effect of Silence for Contralateral ABR Measures

Measure	Source	F	Partial η^2	P (Sig)
Wave V Latency	Silence	4.5	0.072	0.038*
	Silence*	0.008	0.000	0.9
	Tinnitus			
Wave V Amplitude	Silence	0.4	0.007	0.52
	Silence*	1.6	0.026	0.22
	Tinnitus			

* Statistically significant $p < 0.05$ **Effect of Tinnitus Perception on ABR Wave V**

In order to examine the differences of the central auditory nervous system activities with regard tinnitus perception, group differences as a result of tinnitus perception on ABR wave V latency and amplitude before and after silence exposure were analyzed for ipsilateral and contralateral recordings utilizing ANOVA.

Table 9 shows the results of ANOVA analysis of the ipsilateral ABR wave V latency and amplitude. Between subjects' effect of tinnitus perception on the Ipsilateral ABR wave V latency and amplitude revealed no statistically significant effect of tinnitus perception on ABR wave V latency ($F = 0.15$, $p = 0.7$), or amplitude ($F = 0.32$, $p = 0.58$).

Table 9

Between Subjects Effect of Tinnitus Perception on Ipsilateral ABR Measures

Measure	Source	F	Partial η^2	P (Sig)
Wave V Latency	Tinnitus	0.15	0.003	0.7
Wave V Amplitude	Tinnitus	0.32	0.005	0.58

Table 10 shows the results of ANOVA analysis of the contralateral ABR wave V latency and amplitude. Between subjects' effect of tinnitus perception on the contralateral ABR wave V latency and amplitude revealed no statistically significant effect of tinnitus perception on ABR wave V latency ($F = 0.2$, $p = 0.89$) or wave V amplitude ($F = 1.02$, $p = 0.9$).

Table 10

Between Subjects Effect of Tinnitus Perception on Contralateral ABR Measures

Measure	Source	F	Partial η^2	P (Sig)
Wave V Latency	Tinnitus	0.20	0.000	0.89
Wave V Amplitude	Tinnitus	1.02	0.000	0.9

The effects of silence and tinnitus perception on ipsilateral ABR wave V latency are illustrated in figure 8. There was no statistically significant difference

between groups and no statistically significant difference before and after silence exposure on the ipsilateral ABR wave V latency.

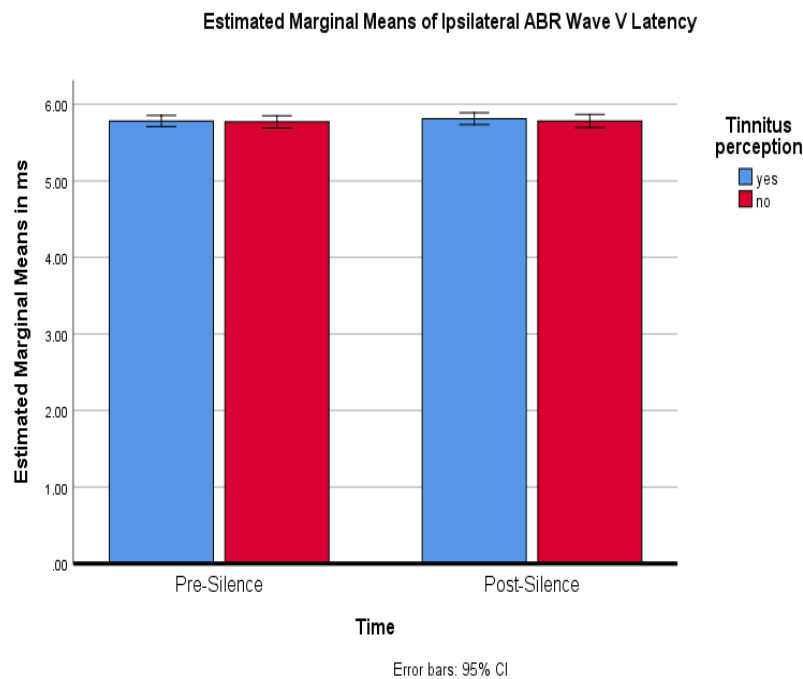


Figure 8. Estimated Marginal Means of Ipsilateral ABR Wave V Latency

Figure 9 illustrates the effect of silence and tinnitus perception on ipsilateral ABR wave V amplitude. There was no statistically significant difference between groups and no statistically significant difference on the ABR wave V amplitude before and after silence exposure.

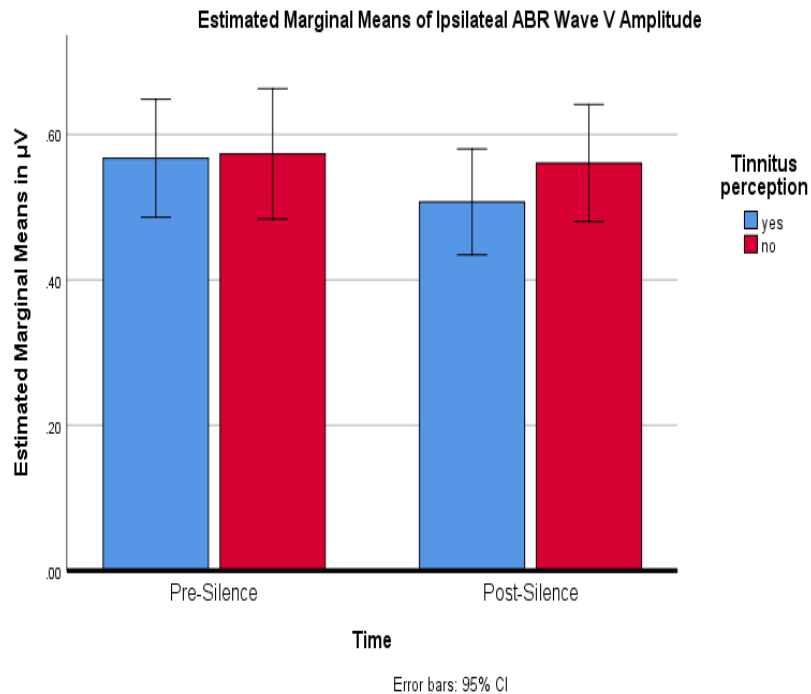


Figure 9. Estimated Marginal Means of Ipsilateral ABR Wave V Amplitude

Figure 10 illustrates the effect of silence and tinnitus perception on contralateral ABR wave V latency. There was no statistically significant difference between groups with regard tinnitus perception, but there was a statistically significant difference on the ABR wave V latency with regard silence exposure ($p=0.038$). Wave V latency increased (were slightly longer in time) for the post-silence recordings than in pre-silence recordings.

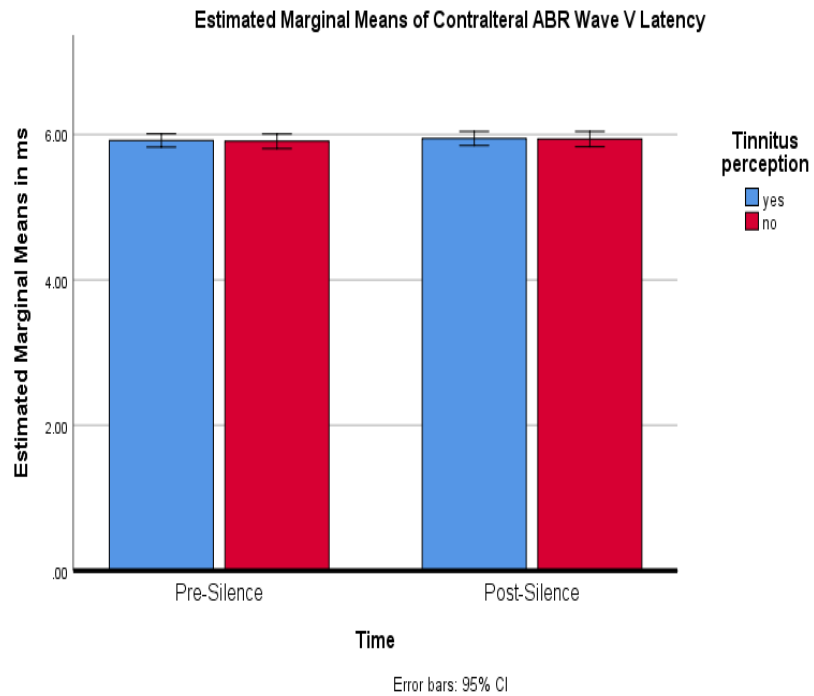


Figure 10. Estimated Marginal Means of Contralateral ABR Wave V Latency

Figure 11 displays the effect of silence and tinnitus perception on contralateral ABR wave V amplitude. There was no statistically significant difference between groups and no statistically significant difference on the contralateral ABR wave V amplitude before and after silence exposure.

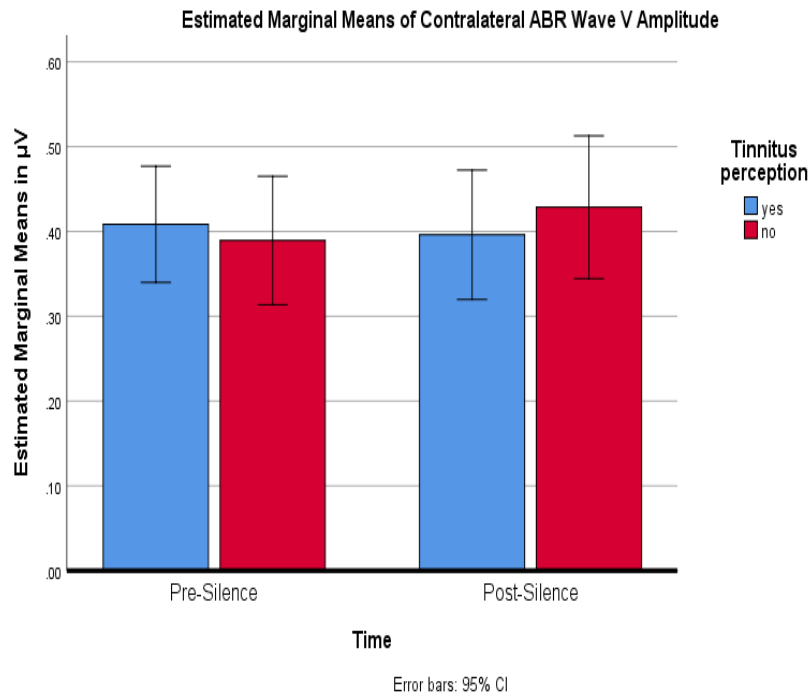


Figure 11. Estimated Marginal Means of Contralateral ABR Wave V Amplitude

AMLR Analysis

To examine the effect of silence and tinnitus perception on AMLR measures, a two-way ANOVA were computed using pre-silence and post-silence recordings for both ipsilateral and contralateral conditions, as the within-subjects variables and tinnitus perception as the between-subjects factor.

Table 11 shows mean and standard deviations of the ipsilateral AMLR Na and Pa waves latencies and Na/Pa amplitude in both pre-silence and post-silence recordings. The mean AMLR Na wave latency was about 16.16 ms and 15.71 ms for tinnitus group in pre-silence and post-silence recordings respectively. AMLR Na wave latency was about 15.99 ms and 15.93 ms for non-

tinnitus group in pre-silence and post-silence recordings, respectively. The tinnitus group shows a trend of shorter ipsilateral Na latency in post-silence recordings than in pre-silence recordings.

Ipsilateral Pa latency was about 28.51 ms and 27.9 for the tinnitus group in pre-silence and post-silence recordings, respectively. Ipsilateral Pa latency was about 29.16 ms and 28.6 for the non-tinnitus group in pre-silence and post-silence recordings, respectively. The tinnitus group showed a trend of shorter Pa latency than does the non-tinnitus group. The mean Na/Pa amplitude was larger for the tinnitus group (1.2 μ V) than for the pre-silence and post-silence recordings of the non-tinnitus group (91 μ V).

Table 11

Ipsilateral AMLR Results for Tinnitus and Non-Tinnitus Groups for Pre-Silence and Post-Silence Conditions

Parameter	Pre-silence		Post-silence	
	Tinnitus	No Tinnitus	Tinnitus	No Tinnitus
	Mean	Mean	Mean	Mean
	SD	SD	SD	SD
Wave Na Latency	16.16	15.93	15.71	15.99
(ms)	1.72	1.67	1.57	1.74
Wave Pa Latency	28.51	29.16	27.9	28.6
(ms)	3.22	3.48	3.0	3.5
Wave Na/Pa Ampl	1.2	0.91	1.2	0.92
((μ V)	0.54	0.34	0.57	0.23
SD= standard deviation; Ampl = Amplitude				

Table 12 shows the mean and standard deviations of the contralateral AMLR Na and Pa waves latencies and Na/Pa amplitude in both pre-silence and post-silence recordings. The mean contralateral AMLR Na wave latency for the tinnitus group was about 16.6 ms and 16.2 ms for pre-silence and post-silence conditions respectively. The mean contralateral AMLR Na wave latency for the non-tinnitus group was about 16.3 ms and 16.5 ms for pre-silence and post-silence conditions respectively. The mean contralateral latency for AMLR wave

Pa for the tinnitus group was about 29.02 ms in the pre-silence condition, which is slightly longer than 28.48 ms in the post silence condition. The mean contralateral AMLR Pa wave latency for the non-tinnitus group was about 29.86 ms in the pre-silence condition and 29.5 in the post-silence condition.

The mean contralateral Na/Pa amplitude for tinnitus group was 1.2 μ V and 1.3 μ V for the pre-silence and post-silence recordings respectively, which is larger than that for non-tinnitus group 0.91 μ V and 1.1 μ V in pre-silence and post-silence recordings.

Table 12

Contralateral AMLR Results for Tinnitus and Non-Tinnitus Groups for Pre-Silence and Post-Silence Conditions

Parameter	Pre-silence		Post-silence	
	Tinnitus	No Tinnitus	Tinnitus	No Tinnitus
	Mean	Mean	Mean	Mean
	SD	SD	SD	SD
Wave Na Latency	16.6	16.3	16.2	16.5
(ms)	1.9	1.5	1.8	1.5
Wave Pa Latency	29.02	29.86	28.48	29.5
(ms)	3.47	3.77	3.3	3.44
Wave Na/Pa Ampl	1.2	0.91	1.3	1.1
((μ V)	.84	0.39	0.36	0.9
SD= standard deviation; Ampl = Amplitude				

Effect of Silence on AMLR Measurements

In order to examine the changes on the central auditory nervous system as a result of a brief period of silence, Within Subjects' effects on AMLR Na/Pa waves latencies and Na/Pa amplitude before and after silence exposure were analyzed for ipsilateral and contralateral recordings utilizing ANOVA.

Table 13 shows the results of ANOVA analysis of the ipsilateral AMLR waves latencies and amplitude. Within subjects' effect of silence on the Ipsilateral

AMLR waves revealed no statistically significant effect of silence on AMLR Na latency ($F = 0.84, \rho = 0.36$) or Na/Pa amplitude ($F = 0.02, \rho = 0.97$). However, Pa latency approached statistical significance ($F = 3.91, \rho = 0.053$); as the mean Pa latency was shorter for the post-silence recordings than pre-silence recordings as hypothesized. There was no interaction effect of silence and tinnitus for Na latency ($F = 1.53, \rho = 0.22$), Pa latency ($F = 0.002, \rho = 0.97$), nor Na/Pa amplitude ($F = 0.001, \rho = 0.98$).

Table 13

Within Subjects Effect of Silence for Ipsilateral AMLR Measures

Measure	Source	F	Partial η^2	P (Sig)
AMLR Na Latency	Silence	0.84	0.014	0.36
	Silence* Tinnitus	1.53	0.026	0.22
AMLR Pa Latency	Silence	3.91	0.063	0.053^
	Silence* Tinnitus	0.02	0.000	0.9
AMLR Na/Pa Amplitude	Silence	0.002	0.000	0.97
	Silence* Tinnitus	0.001	0.000	0.98
^ Approached statistical significance				

Table 14 shows the results of ANOVA analysis of the contralateral AMLR waves latencies and amplitude. Within subject effect of silence on the Ipsilateral AMLR wave Na latency revealed no significant effect of silence on AMLR wave Na latency ($F = 0.13, \rho = 0.72$), Pa latency ($F = 1.31, \rho = 0.26$), nor Na/Pa amplitude ($F = 0.13, \rho = 0.72$). There was no interaction effect of silence and tinnitus for Na latency ($F = 1.81, \rho = 0.18$), Pa latency ($F = 0.05, \rho = 0.18$), nor Na/Pa amplitude ($F = 1.8, \rho = 0.19$).

Table 14

Within Subjects Effect of Silence for Contralateral AMLR Measures

Measure	Source	F	Partial η^2	P (Sig)
AMLR Na Latency	Silence	0.13	0.002	0.72
	Silence* Tinnitus	1.81	0.031	0.18
AMLR Pa Latency	Silence	1.31	0.022	0.26
	Silence* Tinnitus	0.05	0.001	0.8
AMLR Na/Pa	Silence	.13	0.002	0.72
Amplitude	Silence* Tinnitus	1.8	0.030	0.19

Effect of Tinnitus Perception on AMLR Measures

In order to examine the overall group difference and the changes in the central auditory nervous system as a result of tinnitus perception, group differences as a result of tinnitus perception on AMLR waves latency and

amplitude before and after silence exposure were analyzed for ipsilateral and contralateral recordings utilizing ANOVA.

Table 15 shows the results of ANOVA analysis of the ipsilateral AMLR waves latencies and amplitude. Between subjects' effect of tinnitus perception on the Ipsilateral AMLR analysis revealed no statistically significant group difference as a result of tinnitus perception on AMLR Na latency ($F = 0.005, \rho = 0.95$), Pa Latency ($F = 0.74, \rho = 0.4$). However, Ipsilateral Na/Pa amplitude revealed a statistically significant difference between groups as a result of tinnitus perception ($F = 0.74, \rho = 0.009$) with larger mean amplitude observed in the tinnitus group as hypothesized in both pre-silence and post-silence recordings. This means that Na/Pa amplitudes were larger in subjects with tinnitus perceptions across pre-silence and post-silence conditions.

Table 15

Between Subjects Effect of Tinnitus Perception on Ipsilateral AMLR Measures

Measure	Source	F	Partial η^2	P (Sig)
AMLR Na Latency	Tinnitus	0.005	0.000	0.95
AMLR Pa Latency	Tinnitus	0.74	0.013	0.4
AMLR Na/Pa Amplitude	Tinnitus	7.4	0.113	0.009**

** Statistically significant $\rho < 0.01$

Table 16 shows the results of ANOVA analysis of the contralateral AMLR waves latencies and amplitude. Between subjects' effect of tinnitus perception on the Ipsilateral AMLR analysis revealed no statistically significant group difference as a result of tinnitus perception on AMLR Na latency ($F = 0.00$, $\rho = 0.98$), Pa Latency ($F = 1.3$, $\rho = 0.26$). However, contralateral Na/Pa amplitude approached statistical significant difference between groups as a result of tinnitus perception ($F = 3.82$, $\rho = 0.056$) with larger mean amplitude observed in the tinnitus group in pre-silence and post-silence recordings as hypothesized.

Table 16

Between Subjects Effect of Tinnitus Perception on Contralateral AMLR Measures

Measure	Source	F	Partial η^2	P (Sig)
AMLR Na Latency	Tinnitus	0.000	0.000	0.98
AMLR Pa Latency	Tinnitus	1.3	0.022	0.26
AMLR Na/Pa Amplitude	Tinnitus	3.82	0.062	0.056 [^]

[^] Approached statistical significance

Figure 12 illustrates the effect of silence and tinnitus perception on ipsilateral AMLR Na latency. There was no statically significant difference between groups and there was no statically significant difference on the ipsilateral AMLR Na latency before and after silence exposure.

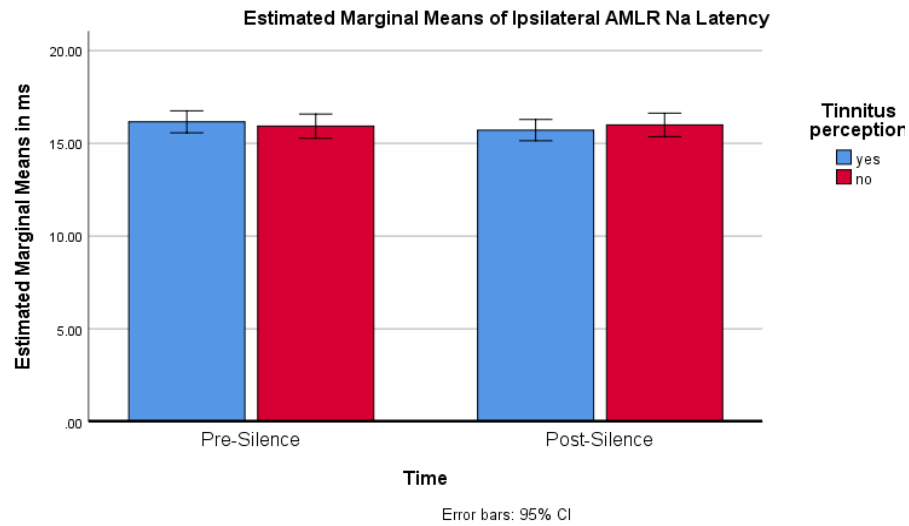


Figure 12. Estimated Marginal Means of Ipsilateral Na Latency

Figure 13 shows the effect of silence and tinnitus perception on ipsilateral AMLR Pa latency. There was no statistically significant difference between groups and there was no statistically significant difference on the ipsilateral AMLR Pa latency before and after silence exposure.

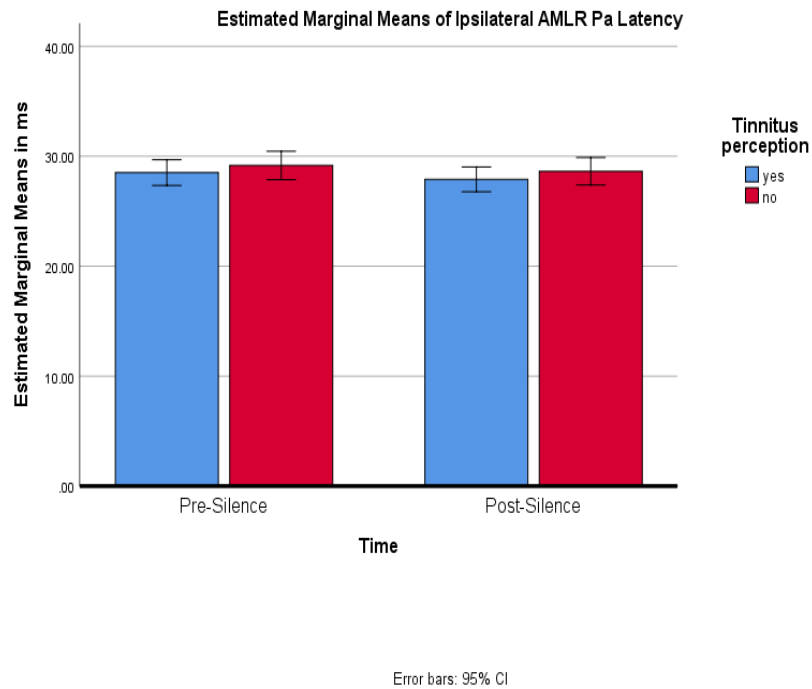


Figure 13. Estimated Marginal Means of Ipsilateral Pa Latency

Figure 14 illustrates the effect of silence and the overall group difference as a result of tinnitus perception on ipsilateral AMLR Na/Pa amplitude. There was a statistically significant difference between groups; however, there was no statistically significant difference on the AMLR Na/Pa amplitude before and after silence exposure.

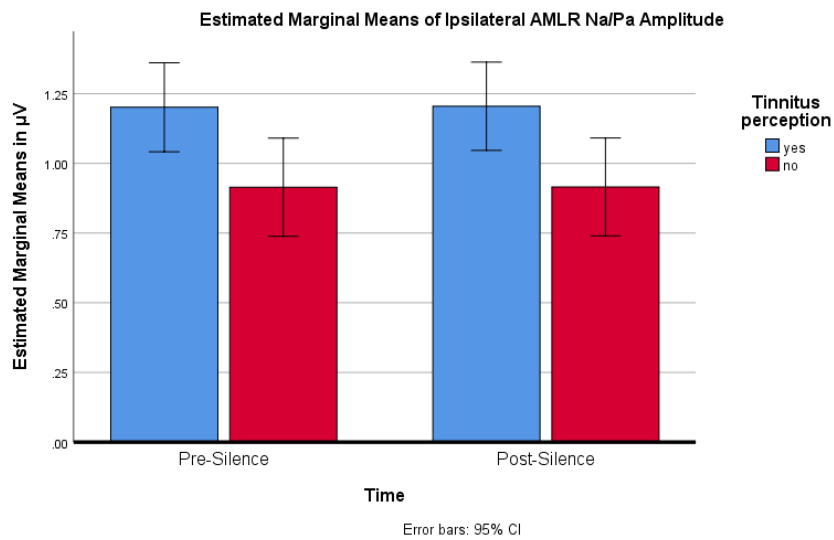


Figure 14. Estimated Marginal Means of Ipsilateral Na/Pa Amplitude

Figure 15 displays the effect of silence and tinnitus perception on contralateral AMLR Na latency. There was no statistically significant difference between groups and there was no statistically significant difference on the AMLR Na latency before and after silence exposure.

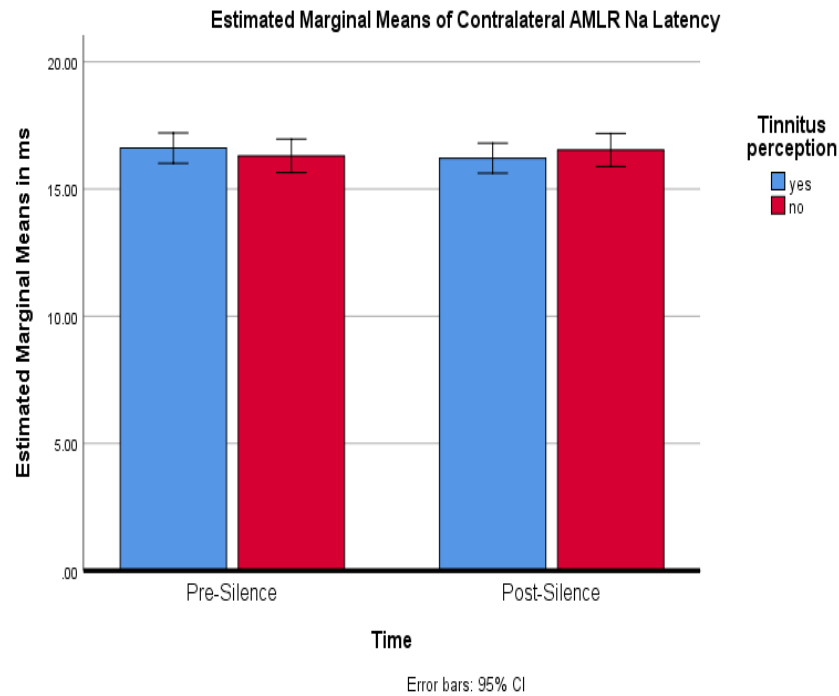


Figure 15. Estimated Marginal Means of Contralateral Na Latency

Figure 16 illustrates the effect of silence and tinnitus perception on contralateral AMLR Pa latency. There was no statistically significant difference between groups and there was no statistically significant difference on the AMLR Pa latency before and after silence exposure.

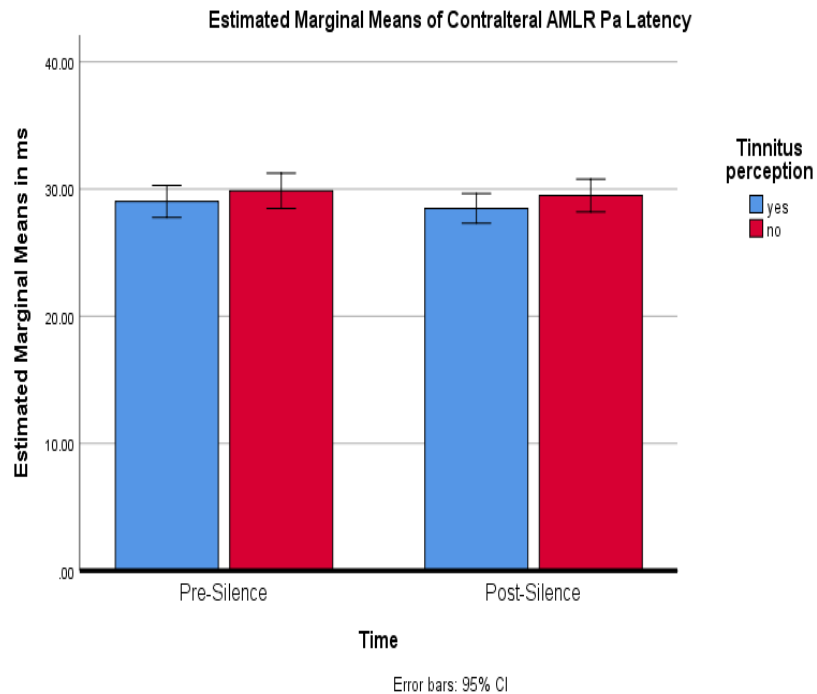


Figure 16. Estimated Marginal Means of Contralateral Pa Latency

Figure 17 shows the effect of silence and the overall group difference as a result of tinnitus perception on contralateral AMLR Na/Pa amplitude. There was a main effect for tinnitus perception as the mean Na/Pa amplitude was larger in tinnitus group than the non-tinnitus group; however, this difference did not reach statistical significance. There was no statistically significant difference on the AMLR Na/Pa amplitude before and after silence exposure.

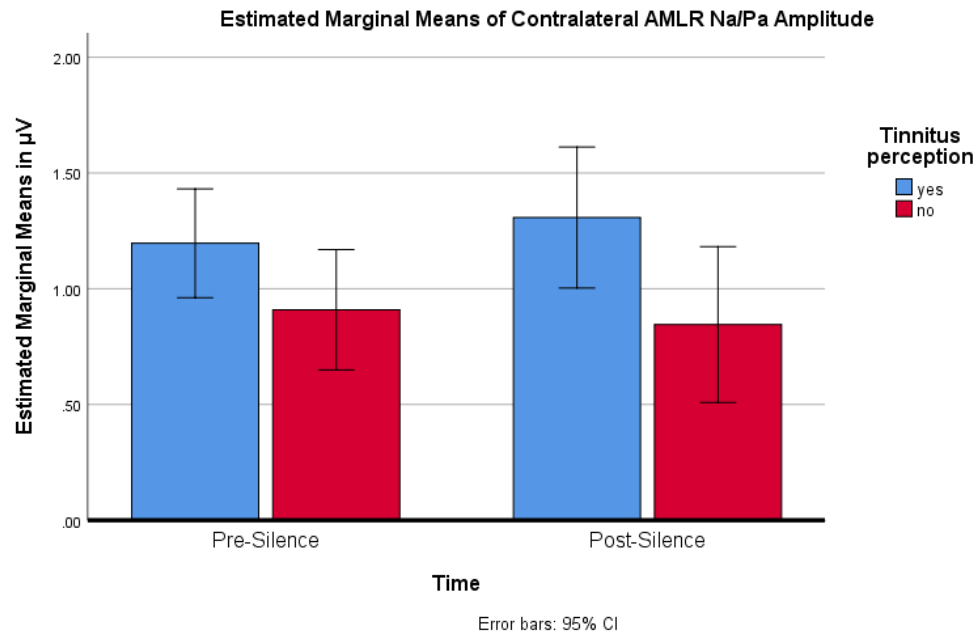


Figure 17. Estimated Marginal Means of Contralateral Na/Pa Amplitude

CHAPTER V

DISCUSSION

The aim of this study was to:

- Examine the effect of silence (a brief period of auditory deprivation) on the emergence of temporary perception of tinnitus-like sounds in normal hearing subjects while controlling for the role of directed auditory attention.
- Document the possible changes along CANS reflected in the latency and amplitude of ABR and AMLR waves after a brief period of silence. These changes would be compared between subjects who had the perception of tinnitus emerging after sitting in silence and in subjects who did not perceive tinnitus after a brief period of silence exposure.

A group of 60 normal hearing adult female subjects were included in this study. Prior to determining enrollment eligibility, all the subjects were audiotically examined to document normal hearing. Normal hearing sensitivity was defined as a hearing level less than 25 dB at each frequency examined, from 250 Hz to 8 kHz associated with type “A” tympanogram. All participants completed a general health questionnaire prior to testing and a silence questionnaire at the end of the AEPs/silence testing session.

This study did not control for race, which was not considered to be an exclusionary factor; the majority of the subjects in this study were white. Tucker et al (2005) in a sample of 120 normal hearing individuals, reported significant racial difference in which tinnitus was most commonly perceived among Caucasians (78%) than African Americans (38%).

Effect of Silence on The Emergence of Tinnitus Perception

Incidence of tinnitus. The results of this study support the hypothesis that normal hearing subjects can experience temporary perceptions of tinnitus-like sounds when exposed to a brief period of silence. About 55% of the participants in this study perceived tinnitus-like sounds after silence. These findings were in agreement with the previous studies, but the number of normal hearing subjects perceiving tinnitus-like sounds were lower than that reported by the previous studies. The mean overall tinnitus perception reported by Tucker et al. (2005) in Caucasian and African-Americans was 64% with 78% of Caucasians reporting tinnitus perceptions compared to 38% of African-Americans. Knobel & Sanchez (2008) revealed that the overall tinnitus perception with auditory attention in their participants was 68.2%, which decreased to 45% with visual attention and 19.7% with cognitive tasks. Del Bo et al. (2008) showed that 83% of their participants experienced tinnitus in a silent environment. Heller & Bergman (1953) reported that 94% in self-reported normal hearing subjects participated in their study experienced tinnitus.

A possible explanation of the difference between the results of the present study and the previous studies is the level of auditory attention towards the tinnitus perception. In the present study attention was directed away from tinnitus by instructing the subjects that the study was about silence and its effect on the auditory system. Knobel & Sanchez (2008) highlighted the important role of auditory attention on the perception of tinnitus-like sound after exposure to silence in normal hearing subjects with no tinnitus complaints. In their study, the overall tinnitus perception when focusing attention on the auditory system was 68.2%, but when subjects were instructed to focus on the visual system only, 45.5% perceived tinnitus, which decreased to 19.7% during a cognitive task. The results of the present study are in agreement with the results of Knobel and Sanchez as 55% of subjects of current study perceived tinnitus while controlling for directed auditory attention.

Additionally, the age range for the subjects who participated in present study was lower than the age range for the subjects who participated in Knobel and Sanchez (2008) study. The age range for the subjects in the present study included young adults (18- 40 years) whereas, Knobel and Sanchez's participants' ages ranged from 18 to 65 years old.

The difference of the current study's results from those of Heller and Bergman might result from the fact that the participants of the Heller and Bergman study "self-reported" normal hearing sensitivity. Thus, some of their subjects might have had some undetected hearing loss, which might have led to

a higher tinnitus perception in those individual as already pointed out by Tucker et al (2005) and Knobel and Sanchez (2008).

Thus, based on the findings of the present study, normal auditory systems are producing a low-level tinnitus-like sounds, which can be perceived by individuals in sufficiently quiet environment.

Types and frequency of perceived tinnitus sounds. The majority of the present study subjects who reported tinnitus during silence, perceived more than one tinnitus-like sound. Eight out of thirty-three subjects perceived solely heartbeat or pulse sounds. The remaining subjects reported hearing more than one sound that included at least one tinnitus sound other than pulsatile or heartbeat sounds. The most common sounds reported in this study other than heartbeat and pulse was hum (30%) and buzz (27%) sounds. In contrast, Tucker et al. (2005) reported that ringing was the most common sound perceived during silence exposure (57%) followed by buzz (21%), pulse (22%), and heartbeat (21%). Whereas, hum and buzz were the most common sounds perceived during silence exposure in Heller & Bergman (1953) study.

Effect of Silence on the Neural Pattern of the CANS

As discussed earlier in Chapter 2, auditory deprivation can affect the function in the auditory system in two ways, both of which can induce tinnitus (Møller, 2011). First, auditory deprivation can alter the excitatory-inhibitory balance; hence increase the gain in the auditory nervous system. Second, auditory deprivation can also activate neural plasticity. Sound deprivation can

occur as a result of pathologies of the ears or the auditory nerve, as well as lack of environmental sounds such as sitting in the sound treated room for a brief period of time. Thus, silence exposure can alter the excitatory-inhibitory balance and induce neural plasticity that cause increased gain in the central auditory functions. These alterations of the auditory functions as a result of silence exposure can be depicted as changes in the amplitude and latencies of AEPs waveforms.

In order to examine the effect of silence exposure on different levels of the auditory nervous system, ABR and AMLR waveforms were analyzed before and after silence exposure to monitor any changes in neural activities as a result of auditory deprivation.

Effects of silence on ABR waveform. The results of the current study revealed that exposure to a brief period of silence have an effect of on ABR wave V latency. Findings in this study revealed a statistically significant difference of the contralateral ABR wave V latency ($p = 0.038$). However, ipsilateral ABR wave V showed some alteration in the latency as a result of silence exposure, these changes did not reach a statistically significant level ($p = 0.09$). There was no statistically significant difference of ABR wave V amplitude as a result of silence exposure in the ipsilateral or in the contralateral recordings. There was also no statistically significant interaction between silence and tinnitus on ABR wave V latency and amplitude ipsilaterally or contralaterally.

Previous studies cited in this study that examined the effect of silence on temporary tinnitus perception, did not examine the effects of those perceptions on the ABR waveforms. The results of current study suggest that auditory deprivation as a result of silence exposure may have an impact on ABR wave V generators as noticed from the significant increase in the latency of the contralateral wave V and the trend of increased latency on ipsilateral wave V.

This finding suggests that silence exposure can alter the functions of the auditory system as indicated by increased latency of the contralateral ABR wave V. However, one of the factors that might have influenced the data reaching more evident statistically significance is the duration of silence exposure. Ten minutes of silence exposure may not be long enough to produce sufficient synchronous neuroplastic changes in the central auditory function in the participants in this study. Future studies need to examine the effects of longer periods of silence on ABR waveforms.

Effects of silence on AMLR waveform. AMLR is an objective electrophysiologic measure of the central auditory functions arises from generators above the level of the lower brainstem. The results of the current study revealed no statistically significant difference of AMLR waves Na, Pa latencies or Na/Pa amplitude as a result of silence exposure in ipsilateral and contralateral recordings. However, there was a trend of decreased mean AMLR ipsilateral Pa wave latency in post silence recordings compared to pre-silence

recordings especially in the tinnitus group, with this trend approaching statistical significance ($p = 0.053$).

This trend of decreased Pa latency after silence exposure may be an indicator of initial increase in gain in the central auditory functions at the level of neurogenic generators of AMLR Pa wave after exposure to a brief period of silence (ten minutes). There was no statistically significant interaction between silence and tinnitus on AMLR waves latencies and amplitude either ipsilaterally or contralaterally.

This preliminary finding suggests that exposure to a brief period of silence does alter the neural functioning of the central auditory neural pathway at the level of AMLR Pa wave generators to some extent. This finding supports previous findings (Dos Santos Filha et al., 2015; Eggermont & Roberts, 2004), which indicate involvement of inferior colliculus, thalamic, and higher cortical structures in tinnitus generation.

However, previous silence studies discussed in the literature review (Del Bo et al., 2008; Knobel & Sanchez, 2008; Tucker et al., 2005) reported the emergence of temporary tinnitus perception within the first five minutes of silence. Ten minutes of silence (sensory deprivation) in the present study protocol may have not been sufficient to cause the significant alteration in central neural pathway enough to inflict more evident statistically significant changes in AMLR and ABR waveforms.

There is paucity on research on the effect of silence on central auditory pathway and AEPs waveforms. To the investigator's knowledge, the present study is the first research study that documents the effect of ten minutes of silence on AEPs waves amplitude and latencies. Additional research is needed to examine the effects of brief periods of silence on AEPs waveforms to further our understanding of the contribution of different levels of CANS on tinnitus perception.

The Emergence of Tinnitus Perception and AEPs

The current study hypothesized that tinnitus-like perception after a brief period of silence was due to a temporary hearing deprivation that caused a brief change in the neural firing patterns along the central auditory system. The participants in this study had normal hearing thresholds, which suggest that tinnitus-like sounds experienced by those subjects were not triggered by problems in the auditory periphery. Hence, it was hypothesized that these changes were aroused from the CANS not the cochlea. Generally, AEPs are used to examine the synchronous discharge of fibers in the auditory pathway and to identify the presence of abnormal neural activities. Hence, AEPs including ABR wave V and AMLR Na/Pa waves latency and amplitude were utilized in this study to examine any possible changes along the central auditory pathway as a result of silence exposure and subsequent tinnitus-like sound perception.

This study utilized ABR and AMLR testing to distinguish between peripheral and central origin of tinnitus-like perception after a brief exposure to

silence. ABR testing provides an objective electrophysiological measure of auditory nerve and the brainstem auditory pathway. AMLR testing provides an objective electrophysiological measure of the subcortical and cortical central auditory pathway.

Effect of tinnitus perceptions on ABR. The results of the current study found no statistically significant differences in ABR wave V amplitude and latency as a result of tinnitus perception. These results indicate that tinnitus perception reported after a brief period of silence is not associated with changes within the auditory pathway up to the level of the brainstem.

These findings are in agreement with Barnea, Attias, Gold, & Shahar (1990) who reported no difference in ABR waves in 17 normal hearing subjects with tinnitus enrolled in their study compared with 19 normal hearing subjects without tinnitus. Similarly, these results are in agreement with Gerken et al. (2001) who compared results of ABR test in 9 hearing impaired subjects with tinnitus with that of 11 normal hearing subjects without tinnitus. Gerken and colleagues reported significant difference between latency of wave VII in the two groups and reported that there were no significant differences in latencies of earlier waves and no significant differences of amplitudes of all waves between the two groups. Also, Nemati et al. (2014) reported no difference in ABR wave latency between normal hearing subjects with and without tinnitus.

In contrast to these results, Singh et al. (2011) reported prolongation of wave I latency in the tinnitus ears of their study group, compared with controls.

Also, the authors reported shortening of wave V latency, I–III and I–V inter-peak latencies in the tinnitus ears, compared to the control group. Conversely, Kehrle et al. (2008) identified significant enhanced V/I amplitude ratio as well as increased latencies of waves I, III, and V in their tinnitus group compared to the non-tinnitus group who participated in their study, although the values for both groups were within normal limits. Similarly, Gu et al. (2012) reported elevated V/I and III/I amplitude ratios in tinnitus subjects compared to age, gender, and threshold-matched non-tinnitus subjects participated in their study.

The results of the present study did not capture any difference in ABR wave V latency as a result of a temporary tinnitus perception. The inconsistent relationship of the ABR activities and tinnitus reported in literature might be related to the underlying etiology of tinnitus and presence of minimal hearing loss in the investigated samples.

Effect of tinnitus perceptions on AMLR. The role of AMLR as an objective measure for tinnitus has not been extensively investigated in the literature. Results of the current study showed no statistically significant differences in AMLR Na or Pa wave latencies between groups as a result of tinnitus perception. However, this study's findings revealed a statistically significant difference in the ipsilateral Na/Pa wave amplitude between tinnitus and non-tinnitus groups ($p = 0.009$), and approached significance in the contralateral recordings ($p = 0.056$), in which the tinnitus group exhibited larger Na/Pa amplitude in both pre-silence and post-silence recordings. These findings

indicate that subjects who reported temporary tinnitus perception during the brief silence exposure possessed increased central neural activities compared to the subjects who did not perceive tinnitus.

The results of the current study revealed that tinnitus-like perception has a large enough effect to demonstrate differences in AMLR Na/Pa waves amplitude between groups. Several factors can affect AMLR waveforms amplitude and latency, such as neuronal firing rate, neural synchrony, age, and the presence of hearing loss. In this study, the effect of age, gender and the concomitant effect of hearing loss was controlled for which helped to reduce the confounding effects on these important factors.

The results of the present study are in agreement with the results of Gerken et al. (2001) who reported enhanced AMLR amplitudes in 5 of the 9 individuals in the problem-tinnitus group compared to the normal hearing group. Similarly, the present results support the findings of Singh et al. (2011) who reported increased wave Na and Pa amplitudes in the tinnitus group compared with controls, which indicates an alteration in the middle latency response generators.

The findings of the current study does not support the results of Theodoroff et al. (2011) who reported no difference in AMLR waves latency and amplitude between severe-tinnitus and non-tinnitus groups who participated in their study. Possible explanation of the difference of the results in both studies

might be related to the difference in age, hearing thresholds, and tinnitus etiology in both samples

The results of the present study indicate that subjects who perceived tinnitus-like sounds during silence exposure may possess a higher baseline central auditory nervous system activity above the level of the brainstem compared to those who did not perceive tinnitus-like sounds during silence as measured by AMLR Na/Pa amplitude.

Conclusions

This research study investigated the prevalence of tinnitus-like perception after a brief period of silence in female subjects and the possible associated changes along the CANS as a result of these perceptions and silence exposure. Tinnitus was perceived by 55% of the subjects who participated in this study. The protocol controlled for directed auditory attention to sounds. Larger AMLR Na/Pa amplitude in subjects who perceived tinnitus in both pre-silence and post-silence recordings indicate that these perceptions are associated with hyperactivity in the CANS that might be masked by the environmental background noise and can be perceived in a sufficiently quiet environment.

Limitation and Future Direction

In this study, sixty females with normal hearing were exposed to ten minutes of silence. The choice of ten minutes was based on the results reported in previous studies that the majority of their subjects perceived tinnitus-like sounds within four minutes of silence. However, ten minutes of silence as

incorporated in this study showed some evidence of increased gain within the central auditory pathway. However, this period may have not been long enough to produce larger significant neuroplastic changes in the auditory pathway. Therefore, it would be beneficial to consider a longer period of silence exposure, which might help revealing more evident results regarding the influence of silence exposure on the CANS.

Other future directions include investigating more variants. The present study was designed to obtain ipsilateral and contralateral AEPs recordings through right ear stimulation. It would be advantageous for future research to investigate both right and left ears and compare the results of right and left ear responses. Also, race was not considered as a factor in this study, with previous research showing that African-Americans are less susceptible to tinnitus-like perceptions after silence exposure. Future research could control the race factor and observe the effect of race on tinnitus-like perceptions and AEPs. Additionally, future research is needed to examine the effect of silence and tinnitus like perceptions on higher levels of the CANS using Auditory Late Response and P300.

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APPENDIX A

GENERAL HEALTH QUESTIONNAIRE

General Health Questionnaire

Start of Block: Default Question Block

Welcome to the survey, these questions will help us learn more about your hearing and general health and to determine your eligibility to participate in this study.

Q1 How old are you?

Q4 Have you ever had?	Yes (1)	No (2)
Recurrent ear infections (1)	<input type="radio"/>	<input type="radio"/>
Severe ear pain (2)	<input type="radio"/>	<input type="radio"/>
Tubes placed in ear (3)	<input type="radio"/>	<input type="radio"/>
Ruptured ear drum (4)	<input type="radio"/>	<input type="radio"/>
Drainage from the ears (5)	<input type="radio"/>	<input type="radio"/>
Dizziness (6)	<input type="radio"/>	<input type="radio"/>
Ringling in the ears (7)	<input type="radio"/>	<input type="radio"/>
Ear injury (8)	<input type="radio"/>	<input type="radio"/>
Head injury (9)	<input type="radio"/>	<input type="radio"/>
Ear surgery (10)	<input type="radio"/>	<input type="radio"/>
Meningitis (11)	<input type="radio"/>	<input type="radio"/>
Thyroid problems (12)	<input type="radio"/>	<input type="radio"/>
Increased anxiety (13)	<input type="radio"/>	<input type="radio"/>
Depression (14)	<input type="radio"/>	<input type="radio"/>

Q2 Do you have a history of hearing loss?

☐ Yes (1)

☐ No (2)

Display This Question:

If Do you have a history of hearing loss? = Yes

Q3 If yes, which ear(s)?

☐ Right ear (1)

☐ Left ear (2)

☐ Both ears (3)

Q5 In the last week, have you been exposed to loud noise?

☐ Yes (1)

☐ No (2)

Display This Question:

If In the last week, have you been exposed to loud noise? = Yes

Q6 If yes, did you wear hearing protection?

☐ Yes (1)

☐ No (2)

Q7 Have you ever had these health conditions?

	Yes (1)	No (2)
Hypertension (1)	<input type="radio"/>	<input type="radio"/>
Diabetes (2)	<input type="radio"/>	<input type="radio"/>
Stroke (3)	<input type="radio"/>	<input type="radio"/>

Q8 Have you ever received these treatments?

	Yes (1)	No (2)
IV antibiotics (1)	<input type="radio"/>	<input type="radio"/>
Chemotherapy (2)	<input type="radio"/>	<input type="radio"/>
High dose aspirin (3)	<input type="radio"/>	<input type="radio"/>

Q9 Please write your assigned number.

Thank you for your time and participation!

End of Block: Default Question Block

APPENDIX B

SILENCE QUESTIONNAIRE

Silence Questionnaire

Start of Block: Default Question Block

The following questions will give you the opportunity to tell us more about your silence experience, please answer the following questions openly and thoroughly.

Q1 Did you hear any sounds during the silence period?

- ☐ Yes (1)
- ☐ No (2)

Skip To: Q3 If Did you hear any sounds during the silence period? = No

Q8 Where did you hear the sounds?

- ☐ Left ear (1)
- ☐ Right Ear (2)
- ☐ Both ears (3)
- ☐ In your head (4)
-

Q9 How soon did you begin to hear the sounds during the silent period?

- ☐ Immediately (1)
 - ☐ Within the first 2 minutes (2)
 - ☐ About five minutes (halfway during the silent period) (3)
 - ☐ About ten minutes, at the end of the silent period (4)
-

Q2 What type of sounds you heard in the silence period (Please choose all that apply)?

- ☐ Buzz (1)
- ☐ Roar (2)
- ☐ Heartbeat (3)
- ☐ Whistling (4)
- ☐ Hum (5)
- ☐ Running water (6)
- ☐ Pulse (7)
- ☐ Hiss (8)
- ☐ Ring (9)
- ☐ Crickets (10)
- ☐ Whiz (11)
- ☐ Other, please specify (12)

Q3 What were you thinking about during the silence period?

Q4 Please enter the assigned number given to you at the beginning of the study

Thank you for your time and participation in this study!

End of Block: Default Question Block